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CARCINOMA OF THE CERVIX DURING PREGNANCY*

W. C. DANFORTH, B.S., M.D., F.A.C.S., EVANSTON, ILL.

(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and of the Evanston Hospital)

ALTHOUGH carcinoma of the cervix is found rarely in pregnant women, we have encountered four such cases. If, in a service of moderate size, four cases are seen, it seems essential to have a clear-cut plan for their management. While the incidence of carcinoma in pregnant women varies in the reports of various writers upon the subject, all agree that it is uncommon. This is partly due to the fact that at the age at which cancer is most common pregnancy is less frequent and, conversely, at the age at which most pregnancies occur, cancer is not often seen. Mauriceau believed that pregnancy was impossible in the presence of carcinoma of the cervix. Wertheim suggests that chemical changes in the cervical secretions may render pregnancy less likely. The presence of a large, necrotic carcinomatous crater upon the cervix renders pregnancy quite unlikely. Obstruction of the cervical canal by masses of tumor tissue may also render pregnancy impossible. Cohnstein believed that the likelihood of pregnancy was increased by the presence of carcinoma, but this has long since been demonstrated to be untrue.

It is highly probable that the overwhelming majority of cancers which are found in pregnant uteri were present before the pregnancy began. Kermauner believed that cancer could not begin during pregnancy and that it always existed before pregnancy began. This is probably true

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in nearly all cases but the impossibility of its beginning during pregnancy is not agreed to by other writers. Courtey believed that pregnancy decreased the rate of growth of the cancer. Later evidence has disproved this. Kermauner insists that proof of the absence of cancer before pregnancy, in cases in which it is found during pregnancy or the puerperium, can only be had by histologic examination of tissue from the cervix taken before the beginning of pregnancy. To this it may be replied that even biopsy is not invariably infallible. We may safely say, however, that only a very small cancer in an advanced pregnancy would permit the assumption that the carcinoma began during pregnancy.

Nearly all pregnant women who have cancer of the cervix are pluriparas. Sarwey remarks that it is rare in a second pregnancy but very exceptional in a first. He could find but seven cases in primiparas. Of 19 cases in the report of Peham and Amreich one only was a primigravida. The others had had from 3 to 16 children. Our experience seems to vary somewhat from that of many writers as one of our patients was a gravida ii and the other three were gravidas iii.

Frequency.—In a recent extensive study by Tagliaferro, the incidence of carcinoma in pregnancy was found to be 0.038 per cent. This was based upon figures gathered from a number of clinics. Sarwey has collected the following figures, to which has been added the figure from our own service.

TABLE I

V. Winckel	10 in 20,000
Stratz	7 in 17,832
Glockner	17 in 26,000
Sarwey	2 in 2,287
Danforth	3 in 20,444

In our own work we have found 3 cases of cancer of the cervix in pregnant women. To these may be added one other case, that of a woman who was delivered at another hospital and who came to us for treatment of carcinoma shortly after. Cancer of the cervix was discovered after labor and had certainly been present during pregnancy. A comparison of the percentage of frequency is found in Table II. Our own incidence is calculated upon the three cases which originated in our service, without including one which was admitted subsequent to labor.

TABLE II

Sarwey (combined figures)	0.06 per cent
Williams	0.056 per cent
Tagliaferro (combined figures)	0.038 per cent
Peham and Amreich	0.0302 per cent
DeLee	0.005 per cent
Danforth	0.0144 per cent
Average	0.0321 per cent

The average incidence of carcinoma of the cervix in pregnancy, as shown in these reports, including our own, was 0.0321 per cent. The incidence of pregnancy in women who have carcinoma of the cervix is much greater. This is quite easily understood as pregnancy is a far more frequent and widely spread condition than cancer and one woman may have a number of pregnancies. The frequency in a number of clinics is shown in Table III.

TABLE III

Weibel	1.0 per cent
Katz	1.18 per cent
Williams	1.57 per cent
Glockner	1.79 per cent
Tagliaferro	1.4 per cent

Influence of Pregnancy on Carcinoma.—Some few writers, as Varnier, have believed that carcinoma was not hastened in its growth but actually hindered. This is known at present to be untrue. The rate of growth is influenced by the greatly increased blood supply of the pregnant uterus and by the histologic character of the tumor itself. As in nonpregnant women, some tumors grow faster than others.

During the puerperium, a cancer, which during pregnancy was small, may grow rapidly. In cases in which delivery *per vias naturales* is still possible, rapid spreading of the tumor may be seen after delivery. This is because of the trauma of labor, the advancing head crushing the carcinomatous tissue, opening lymphatics and blood vessels and forcing malignant cells into areas previously uninvaded. This explains the rapid extension of cancer soon after delivery, a fact which is illustrated by one of the cases here reported. The laceration of the diseased cervix caused by labor, with the consequent opening up of lymphatics and blood vessels, predisposes to sepsis, hemorrhage, thrombosis, and embolism. Even though delivery may take place without operative intervention, labor still is gravely dangerous to the mother. In one of the cases included in this report, a lesion which was quite small during pregnancy grew rapidly after delivery and death followed in a few months.

Effect of Carcinoma upon Pregnancy.—A small carcinoma, especially when confined to the visible portion of the cervix, may cause no trouble and may not disturb the normal progress of the pregnancy. As in nonpregnant women, there may be no symptoms.

Abortion is more frequent in the presence of carcinoma of the cervix and is more likely to occur when the cancer invades the cervical canal. The higher the invasion goes the more likely abortion is to occur. Kiwisch believed that abortion or premature labor always occurred when carcinoma was present. Experience has long since shown that he was wrong.

Occasionally pregnancy may proceed without interruption in the presence of extensive cancer. Placenta previa occurs with greater fre-

quency. The reason for this is not apparent. Rarely, rupture of the uterus may occur when extensive carcinomatous invasion has taken place.

Effect of Carcinoma upon Labor.—A small growth, localized upon one lip of the cervix, may cause no obstruction to labor. This was true in one of our cases, although rapid growth occurred afterward. The situation is quite different with large growths. A large tumor mass may obstruct the advance of the head. A carcinoma completely encircling the cervix or invading a large part of its circumference may render dilatation impossible. On the other hand, if a considerable part of the cervical circumference is free from cancer, sufficient thinning and dilatation of the uninvaded portion may take place to permit the infant to pass. Inertia uteri, which may come on after labor has been in progress for a time, may stop labor, the pregnancy then continuing indefinitely.

In some cases in which spontaneous delivery occurs there may be severe injury to the diseased portion of the cervix. Deep lacerations may be caused by the advancing head and these may be followed by severe hemorrhage. Later results are sepsis, thrombosis, or embolism. An extensive carcinomatous invasion is prone to be accompanied by infection, especially if areas of necrosis are present. Dangerous sepsis in the puerperium is especially to be feared.

The pressure of the fetal head and body upon the cancer crushes it and perhaps causes more or less solution of continuity in its tissue mass. This sets free malignant cells and at the same time opens up lymphatic and blood channels. Cancer cells may be forced through the blood and lymph vessels by the trauma of labor into areas not yet invaded. Our observation of extremely rapid progress of cancer growth after labor is in accord with that of a number of writers.

The four cases which we have seen are here briefly reported.

CASE 1.—(No. 50798.) Patient aged thirty-five years, para ii, May 2, 1925. Pregnant five months. Cervix twice normal size, hard, friable, bled easily. The uterus was of the size of a four to five months' pregnancy. Section of a bit of tissue removed for diagnosis was described by the pathologist as follows: "Sections of cervix disclose infiltrating island masses and strands of typical tubular epithelium with many mitotic figures in the nuclei. Sections of the endometrium disclose a similar structure." (J. L. Williams.)

The uterus was emptied on May 9, 1925, by abdominal hysterotomy, the intention being to irradiate as soon as possible after this operation. The operation was followed by infection and peritonitis, death occurring May 20.

CASE 2.—(No. 84500. Dr. C. E. Galloway.) A woman of thirty-seven years was admitted to the hospital July 24, 1930. Two normal labors at term. One pregnancy ended at eight months because of placenta previa. One pregnancy terminated at six months because of toxemia. Menstruation began at the age of fourteen, twenty-eight-day type, lasted four days. Last menstruation June 28.

The cervix was large, long, and was deeply lacerated upon the left side. At the base of the healed laceration was a small lesion, which, upon biopsy, proved to be carcinoma.

On July 25, as it was thought that an early pregnancy might be present, curettage was done preceding the use of radium. A very small product of conception was obtained. Irradiation was then carried out, 3,500 mg. hours being given. Radium was introduced into the cervical canal, screened by 1 mm. of brass and rubber, and a palisade of needles each containing 10 mg. was placed about the periphery of the growth. An uneventful recovery followed. This woman is still alive and free from demonstrable recurrence.

CASE 3.—(No. 103877.) Patient aged twenty-three, January 7, 1934. This case was seen through the courtesy of Dr. L. W. Mason. Four months earlier she had had her second child, the labor passing without incident. Four years before she had a lesion upon the cervix which was regarded as syphilitic and at that time had a four-plus Wassermann. Prolonged antisyphilitic treatment caused the disappearance of the Wassermann reaction. A one-plus positive Wassermann returned during pregnancy and remained after delivery. The child was normal and cord blood gave no Wassermann reaction. At delivery her physician noted a very small ulcer upon the cervix. Bleeding began early in the puerperium and continued at intervals.

When seen by me a large growth was found which involved the whole cervix. It bled easily upon touching and had all of the palpatory characteristics of cancer. Microscopically a highly anaplastic type of epidermoid cancer was found. On January 10 the accessible portion of the cancer was electrocoagulated. This was followed at once by 3,500 mg. hours of radium, the radium being applied within the cervix and in needles about the periphery. The result was unsatisfactory and death followed on Oct. 10, 1934.

CASE 4.—(No. 116162.) Patient aged thirty-six years, December 28, 1935. Seen through the courtesy of Dr. George Turnbull. Her second pregnancy had reached four months. The first terminated at seven months. Last menstruation August 17. For three months she had had irregular bleeding and had feared she might miscarry. The uterus was enlarged to the size of a four months' pregnancy. Aschheim-Zondek was positive. The cervix was enlarged, indurated, bled easily when touched. Two polyps were visible at the external os. A small bit of tissue was obtained by means of a punch forceps. This was examined by Dr. F. D. Gunn, who reported as follows: "Squamous cell carcinoma of the cervix showing predominance of cells of the basal type and a high degree of anaplasia in some areas." (Grade III.)

As the tumor had broken down but little and the invaded area appeared far cleaner than is the case with most cancers it was decided to risk preliminary emptying of the uterus. This was done on December 20, a short incision being made at the fundus, as far as possible away from the cancerous area. An uneventful recovery followed and upon December 28 the accessible part of the cancer was electrocoagulated. Irradiation immediately followed, 5,000 mg. hours, being given by means of the Curie colpostat, 50 mg. of radium being also placed in the cervical canal screened in 1 mm. of aluminum. An uneventful recovery followed and when the woman was examined late in June the cervix was entirely healed and the uterus freely movable. Sufficient time has not elapsed to be certain of cure.

DIAGNOSIS

It is possible for the cancer to reach an advanced stage without giving any symptoms. Every experienced gynecologist has seen cases of carcinoma of the cervix in nonpregnant women who have had no symptoms which caused them to believe they were not wholly normal until the cancer had attained an advanced state of growth. In general, diagnosis during pregnancy is rather more difficult than at other times. This is

partly because of the change in size, color and consistency of the uterus. Small blood losses may be looked upon by the patient as threatened abortion and a watery discharge may be confused with the increased vaginal discharge common in pregnancy. On the other hand, the woman who suspects pregnancy often comes to the physician early. The extremely conservative management of abortion which is advocated today may cause the physician to overlook an early cancer. An area of induration in the cervix should raise at once the suspicion of carcinoma. This may be more easily detected because of the soft surrounding cervical tissue. This point has been remarked upon by Tagliaferro, Sarwey and Bar. In our three patients who were seen during pregnancy, the contrast between the hard indurated carcinomatous cervix and the soft normal pregnant cervix was striking. The importance of early diagnosis is so great that, should the character of the lesion be not at once apparent, biopsy should be done. This has been recommended by Sarwey and a number of writers since his work appeared including Tagliaferro. This may be done by a punch forceps or by the electrically heated loop. If the latter is used, the risk of spreading cancer is negligible. If the former is used, the area from which the tissue is taken may be touched with formalin. In any case the danger of harming the woman is slight and not to be considered in view of the paramount importance of timely diagnosis. Advanced carcinoma, presenting cauliflower-like masses, extensive induration, or perhaps a necrotic crater, presents little diagnostic difficulty.

During labor, if the cancer has not been discovered earlier, its presence may be suspected when labor does not progress and a thick, indurated and rigid cervix is found. Advanced carcinoma has been confused with placenta previa, the spongy masses being taken for placental tissue. Such cases have been reported by V. Franqué, Pestalozza, Kermauner, and others. The history here is important. The occurrence of previous moderate bleedings caused by slight disturbance, coitus, defecation, the bleedings occurring at intervals over a considerable part of the pregnancy, speaks for cancer.

The hemorrhage caused by placenta previa is much more profuse. It is entirely independent of trauma and may occur when the woman is completely quiet. The palpatory findings aid in differentiation. In placenta previa the cervix is normal and the placenta may be recognized in the lower uterine segment. The head is held at a higher level by the placental mass. If cancer is present the characteristic carcinomatous induration should be detected by the examining finger in the cervix and cervical canal. If extensive cancerous involvement is present the masses of malignant tissue should be easily recognized.

Cases have been reported (Floel, Hofmeyer) in which cancer and placenta previa have been found together. In such cases the diagnostic

problem is considerably more difficult. Extensive ectropion or a more than normally firm consistency of the cervical tissue may cause carcinoma to be suspected when it is not present.

When carcinoma is accompanied by a very early pregnancy, the recognition of the latter may be difficult. The usual amenorrhea of pregnancy may be masked by the occurrence of bleeding caused by the cancer.

It is essential that the extent of the carcinomatous invasion be determined as exactly as possible in order that management may be most efficiently planned. In early pregnancy, if extension into the parametria has not taken place, mobility of the uterus may not be greatly lessened. In more extensive invasions with necrosis of the tumor surface, the lessened mobility of the uterus may be in part due to inflammatory exudate and not wholly to lateral extension of the cancer. If pregnancy is suspected and is not sufficiently advanced to render recognition easy, the Aschheim-Zondek or Friedman-Schneider tests are very helpful.

PROGNOSIS

The maternal prognosis has changed materially for the better in the past seventy years. Cohnstein found a mortality of 57.1 per cent in cases reported up to 1873. Chantreuil, quoted by Coroenne, collected 60 cases. Twenty-five of these women died in labor. The remainder died during the year of the labor or the following year. Theilhaber found a mortality of 31.5 per cent in the years intervening from 1873 to 1893. The mortality in the cases collected by Sarwey from 1898 to 1907 was 7.5 per cent. Of late years the increasing use of radiotherapy has lessened primary mortality. The increase in permanent cure has not been as striking as the decrease of primary mortality.

The prognosis for the mother is unfavorably influenced because of the rapid progress of the tumor during pregnancy, and during labor by tearing of the abnormal cervix, hemorrhage, and sepsis. During the puerperium the acceleration of tumor growth which is probably due to the trauma of labor again decreases the probability of cure. Early recognition and prompt utilization of radiotherapeutic and operative means have substantially increased the hope of cure. The extremely pessimistic attitude of Pinard and Champetier de Ribes, who considered every pregnant woman with cancer as doomed, irrespective of the type of treatment, is no longer justified.

FETAL PROGNOSIS

In early pregnancy many abortions occur, the fetus thus being lost. Surgical and radiotherapeutic measures utilized in the attempt to eradicate the cancer, sacrifice the lives of some infants and interfere with the normal development of others. In pregnancies which have gone to term, fetal life may be sacrificed or injury may occur because of ob-

structed labor caused by the rigid undilatable cervix. In patients delivered vaginally at or near term Tagliaferro points out that the forceps offers a much better outlook for the infant than extraction by the breech. In the former the forceps serves in a sense, as he puts it, as a "protective helmet," while the after-coming head must be forcibly and rapidly brought through the rigid cervix. The best results for the child are obtained by abdominal cesarean section.

In pregnancies other than very early ones, a definite loss of fetal life follows the use of procedures done primarily in the mother's interest. Destructive operations and emptying of the uterus before viability cost a considerable number of fetal lives.

The infant of a markedly cachectic or severely toxic woman may be poorly developed. This will be seen only in advanced cases of cancer in women in late pregnancy. A case described by Cornil is referred to by Coroenne in which cancer was found in the thyroid, peritoneum, frontal bone and left patella of the child.

TREATMENT

The management of carcinoma during pregnancy has changed greatly in the course of the past fifty years. Amputation of the cervix, the removal of tumor masses which might obstruct labor, or cauterization were the only means of treatment at first available. As the mother had little chance for continued life, the chief attempt was to save the fetus. Interruption of pregnancy was found to be dangerous to the mother and was given up. Throughout the discussion available in the literature, experience has drawn a distinction between early and late cancers, or, between those which, when operative treatment is considered, are regarded as operable or inoperable. Again, a definite difference in efficiency of treatment has been noted between early and late pregnancies, or to divide the cases more exactly, those in the first six months and those in the last three. As to management during labor the early reports indicated that those cases which were allowed to go spontaneously into labor and to deliver, if possible, unaided, gave results far superior to those attained in cases terminated operatively, as by dilatation or incision of the cervix followed by extraction. Cohnstein, in 1873, for example, reports a maternal mortality of 50 per cent in cases in which incision of the cervix was employed, with a fetal mortality of 37 per cent. In a series of 9 cases in which craniotomy was done, 6 women died. It is apparent that an expectant management can succeed only in those cases in which the cervix is not so extensively invaded that it cannot dilate, and in which the tumor mass is not large enough to serve as a mechanical obstacle.

Cesarean section gave far better results for the child but many of the mothers died of infection and hemorrhage. The advent of the Porro

cesarean hysterectomy decreased the immediate death rate from sepsis but the maternal loss of life continued to be high from the cancer which remained and continued to grow.

Subtotal hysterectomy had another advantage, in that the removal of the uterine body prevented lochiometra due to closure of the cancerous cervix.

Vaginal hysterectomy was tried by Sarwey and a number of contemporary operators. It was found that, especially in the early months, it was rather more easily done than in nonpregnant women. This was due to the loosening of the fascial attachments of the uterus. It was carried out even in late pregnancy. Sarwey suggested that in the first trimester hysterectomy should be done without emptying the uterus, in the second trimester after emptying the uterus and in the third after vaginal cesarean section. Vaginal hysterectomy appears to have performed one service, for it proved that the earlier operative treatment is carried out, the better the chance of the mother.

The advent of the radical abdominal hysterectomy advocated by Ries and Wertheim brought a further and marked increase in the number of permanent cures. Its immediate mortality was greater than that of vaginal hysterectomy. This procedure came to be used more and more, vaginal hysterectomy occupying a continuously less important place. With the lessening of primary mortality and the increase in permanent cure there came necessarily to be less importance placed upon the life of the infant, unless it had, at the time of intervention, attained viability.

The increasing efficiency of radiotherapy again added to the success with which these difficult cases are managed. As late as 1928, however, Eymer said that the indications and value of this method could not be given. Portes and de Nabias, in cases in which viability had been attained, advised cesarean section, subtotal hysterectomy and irradiation of the carcinomatous stump. The use of any large amount of irradiation carries with it a distinct risk to fetal life, and irradiation in early pregnancy is followed by many abortions. Ikeda reported 7 cases in which irradiation was used in cancer in pregnant women. Two of these aborted and died. Five, irradiated in the sixth and seventh months, had spontaneous deliveries of normal children. Three of them became pregnant again and died of hemorrhage from lacerations of scars. One is disposed to wonder whether a recurrence had not occurred.

It seems agreed today that, except in patients who are quite hopeless, treatment shall be immediately instituted without regard to the child unless the child has attained viability. The choice of treatment is important. In Case 1 of those here reported, an unwise mode of attack was chosen. We had seen no previous case and were unfamiliar with other reported cases. If operative intervention is preferred the type of operation must be chosen. If radiotherapy is elected a choice must be

made between radium and x-ray, or perhaps a combination of these. A combination of surgery and radiotherapy may be wise. The fate of the fetus must be decided. And finally, intelligent management depends upon an appreciation, as definite as may be, of the extent of the growth.

Operative removal is far more successful in early pregnancy. Peham and Amreich report six cures in a total of 19 cases, all of the cured patients having been operated upon in the first half of pregnancy.

Vaginal hysterectomy will naturally find a restricted application because of the relatively small number of operators who can work with facility by this route. Peham and Amreich favor abdominal hysterectomy, and this, except in early cases of limited extent, appears to be the most successful method.

In the first trimester, if operative management is chosen, radical hysterectomy is at once to be carried out without previously evacuating the uterus. The disease and the pregnancy are then at once disposed of. Previous evacuation increases somewhat the chance of diffusion of cancer cells. Operation should be followed by deep x-ray irradiation. If radiotherapy is chosen (and, unless the cancer is an exceedingly early one, this seems the preferable course), irradiation should be done irrespective of the pregnancy. This should be followed by deep x-ray irradiation or by the radium pack if this is available. The fetus will be killed and will probably come away spontaneously. If it does not the uterus may be evacuated six to eight weeks later. When x-ray is used, abortion is caused by alterations in the vessels of the placenta and cord. Abortion following radium is usually due to the capsule in the cervix, which acts as a foreign body.

In the second trimester, if the carcinoma is still operable, radical hysterectomy may be done if the surgical mode of attack is preferred. If irradiation is elected local irradiation by means of radium should be used followed by deep x-ray therapy. The fetus will be destroyed and may be expelled spontaneously later. If this does not occur the uterine body with its contents may be amputated, or if the extent of the lesion permits, complete hysterectomy may be done.

In dealing with Case 4, we quite deliberately evaded this rule simply because the carcinoma seemed to be sufficiently clean in a surgical sense that we might evacuate the uterus prior to irradiation with a fair degree of safety. This avoided the trauma to the cervix which would be caused by a later evacuation of the uterus through the birth canal or the necessity for later operation, and left the field clear for irradiation. It also avoided the possible disturbance of the carcinomatous area by a later operation and permitted the radiotherapy to proceed as in a nonpregnant case. While it succeeded in this case, and I should be inclined to do it again in a similarly favorable case, it cannot be recommended as a routine plan of management.

In the last trimester results of treatment are less satisfactory than in the earlier cases. Upon this point all authors who have written upon the subject agree. Reports of operated cases show that cures are far rarer in late pregnancy than in the first half. In the seventh and eighth months of pregnancy it is well to wait until the child has attained a development which renders extrauterine life fairly possible before beginning treatment, whether this is to be operative or radiotherapeutic. This seems justified by the fact that at this stage of pregnancy the chance of permanently curing the mother by any means is not great. When this time has arrived, the uterus may be emptied and a subtotal hysterectomy done: in short, a Porro operation, with subsequent irradiation by radium and x-ray. Baer's suggestion merits attention. Not over 3,000 mg. hours of local irradiation by means of radium may be given, which will check the growth of the cancer until the child is viable. A Porro operation is then done, followed, after recovery, by complete radiotherapeutic treatment. This cannot be regarded as the best plan for the mother but will save an occasional infant. An alternative procedure is the radical Ries-Wertheim hysterectomy. This is available only when the extent of the growth permits its use. My own preference would be for the Porro operation followed by irradiation.

The reports of the effect of radium upon the fetus vary somewhat. Burnam reports 3 cases in which healthy infants were born after irradiation of a carcinoma of the cervix during pregnancy. Dosage is not stated. The opinion that radium is less harmful to the infant than x-ray is not borne out by the work of Goldstein and Murphy, who report a case of microcephalic idiocy in an infant delivered by a woman who was given 4,400 mg. hours of radium at six months' gestation. This child was followed for a number of years and remained an unteachable idiot. Petenyi reports a similar case after x-ray therapy; the child, however, was not observed over as long a time.

Goldstein and Murphy have collected 106 cases of women who were irradiated during pregnancy. Of these, 74 delivered full-term children. Thirty-eight (51 per cent) of these children showed disturbance of health or development of more or less serious nature. Sixteen of these children were microcephalic idiots. Fifteen of these mothers had been treated with radium. Radium therapy does carry with it a definite risk to the child *in utero*. Goldstein and Murphy believe that, if irradiation is used for carcinoma, the pregnancy should be terminated. Certainly figures like this cause one to hesitate in applying full radiotherapy unless the child is too far from viability to cause it to be an important consideration.

TREATMENT DURING LABOR

Cases of cancer of the cervix in women in labor divide themselves into two groups; those in which the cancer is small and involves only a portion of the cervix, and those in which the cervix is extensively invaded. If a sufficient amount of normal cervix remains to allow enough dilatation to permit the passage of the infant without serious injury to the cervix, labor may be allowed to complete itself spontaneously.

Extensive carcinoma either obstructs delivery completely, or allows the passage of the infant only at the expense of tears of the carcinomatous cervix. Serious hemorrhage, difficult or perhaps impossible to control, is the primary result with serious sepsis probable if the woman survives the labor. If the cancer is sufficiently extensive to be in any sense a problem during labor, delivery should not be attempted from below. Incision or dilatation of the cervix is extremely hazardous and should not be attempted. Two procedures are available. A Porro cesarean section may be done, with complete radiotherapy later. The operation will probably cause a wider diffusion of carcinoma, but it may be remembered that cure at this late stage of pregnancy is improbable in any event. The removal of the uterine body lessens the danger of peritonitis, which is very likely to follow simple cesarean section. Lochiometra is also prevented. The safety of the infant is far greater than if delivery is done from below.

Cesarean section may be done, followed by a Wertheim radical hysterectomy. This can be considered only if the cancer is within operable limits. It is a far more extensive procedure, and, in the greater number of cases, will not be possible. The Porro operation and subsequent irradiation are preferable. In patients operated upon too near the end of pregnancy the percentage of curability is so small that the assumption of a much greater primary operative risk does not seem wise.

CONCLUSIONS

1. The frequency of carcinoma in pregnancy, as estimated from several reports and including our own work, is 0.0321.

2. Pregnancy is unfavorably influenced. Abortions are frequent, placenta previa is more common than in normal pregnancy.

3. Labor may be gravely dangerous and is sometimes impossible.

4. Carcinoma is very rarely transmitted to the fetus, and, unless pregnancy terminates prematurely, it seems to develop as well as in other cases.

5. The results of treatment are far better during the first six months than in the last three.

6. Today irradiation, both by radium and deep x-ray, is the most effective treatment. This should be done at once unless the pregnancy is so far advanced that it is desired to allow the child to attain viability.

7. If full radiotherapy is used, the pregnancy is better terminated because of the risk of serious developmental harm to the infant.

8. A moderate radium dosage may be used to check the growth of the tumor in order that the child may attain viability with less likelihood of harm.

9. Labor may be permitted to begin spontaneously if the cervix has a sufficient uninvaded area to permit dilatation enough for the passage of the child.

10. Incision or dilatation of the carcinomatous cervix is gravely dangerous.

11. If labor is not possible, cesarean section should be done as an elective measure. This should be followed by a Ries-Wertheim radical hysterectomy or subtotal hysterectomy with irradiation of the carcinomatous stump. The latter is favored.

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DISCUSSION

DR. JOSEPH L. BAER.—As a basis for treatment, the carcinoma must be regarded as primary and the pregnancy as a complication, just as with other diseases complicated by pregnancy.

The outstanding treatment in any carcinoma complicated by early or late pregnancy is adequate and competent irradiation. This means 3,000 to 4,000 mg. hr. of radium to the cervix with the same amount of pelvic irradiation or an equivalent amount of deep x-ray therapy.

This treatment in early pregnancy will result in death of the fetus and termination of the pregnancy by abortion, spontaneous or operative. After viability the treatment produces in 40 per cent of the cases fetal defects, such as alopecia, microcephaly and idiocy. Hysterotomy or primary induction of abortion to evacuate an early pregnancy, or cesarean section to rescue a viable fetus while retaining the carcinomatous uterus, has a high mortality, even with subsequent irradiation.

The following condensed outline of treatment is offered: If the pregnancy is less than four months, complete irradiation is safest, regardless of the extent of the carcinoma. Spontaneous abortion usually follows. If not, the uterus can be emptied subsequently, for the irradiated cervix offers little resistance to dilatation. Occasionally, when the lesion is clinically merely suspicious, but is confirmed by biopsy and there is no involvement of the deeper cervix, a skilled operator may attempt radical surgery with subsequent radiation.

If the pregnancy is somewhat less than seven months, the lesion belongs to the clinical Group I and the mother wants the child, it is wise to use local irradiation only. That temporarily stops the disease. When viability is attained, Porro section and then irradiation are indicated. In all other types of lesions with a pregnancy of four to seven months, complete irradiation is advised. Thereafter if spontaneous evacuation of the uterus does not occur supravaginal hysterectomy with removal of the adnexa should be undertaken. When the pregnancy is between seven and nine months and the lesion belongs to clinical Group I, a Porro section should be done with retention of the cervix followed by complete irradiation. In all other types of lesions, preliminary local irradiation of the cervix to minimize infection and retard spread of the carcinoma should be given followed by Porro section, and then final irradiation.

In labor at or near term, where there is a small lesion, spontaneous vaginal delivery should be permitted, followed by complete irradiation. In all other types of lesions of the cervix, Porro section should be performed at once with later irradiation. The less desirable alternative to this is cesarean section followed by the Wertheim operation and subsequent irradiation.

I believe we are ready to discard microscopic classification of carcinoma of the cervix as a guide to treatment. It would be a mistake to deprive a woman of irradiation merely because her squamous carcinoma is regarded as less radiosensitive than the anaplastic type. If an operative procedure is contemplated, it is important to culture the cervical secretions. If the *Streptococcus hemolyticus* is present, radiation must come first.

DR. GEORGE H. GARDNER.—There is still some question whether pregnancy actually has a stimulating effect on carcinoma. According to Stoeckel, who observed only 8 carcinomas in 15,000 pregnant women, nothing was observed after operating on these women which would warrant an assumption that the pregnancy either retarded or hastened the growth.

Since bleeding begins rather early and tends to be free and since most expectant mothers recognize the seriousness of any vaginal bleeding during pregnancy, there is ample opportunity for an early diagnosis and most of these carcinomas must be relatively early lesions, otherwise the woman probably would not have become pregnant. Often the lesion looks worse than it actually is because of the effect of pregnancy hyperemia.

Our experience at Passavant Hospital included only two such cases:

The first, a thirty-nine-year-old multipara, presented a large fibroid, a five months' pregnancy, and a carcinoma, apparently localized to the cervix. She was subjected to complete hysterectomy. Glands were found in the left iliac chain but were not removed. Subsequently she was given deep x-ray radiation. Apparently this therapy was too intensive because she died a year later of an agranulocytosis which was believed to have been induced or aggravated by the x-ray. At autopsy the glands were found to be somewhat larger than at operation and contained metastatic cancer.

The second patient was only thirty years of age. Her cervix was involved by an earlier lesion and her pregnancy was of three months' duration. Dr. Curtis performed a radical Wertheim operation. Although the uterus was freely movable glands were found in the left parametrium and were removed. This patient is receiving deep x-ray radiation and there is no evidence of recurrence, ten months after operation.

DR. HERBERT SCHMITZ.—I would like to add two cases to the series. At Mercy Hospital in 770 carcinomas of the cervix two occurred in pregnant women. One was twenty-eight years of age, a para ii, with a clinical Group III lesion in the last trimester of pregnancy. The other was aged thirty-six, para iv, a clinical Group IV lesion. Both of these were treated by cesarean section. Viable children were obtained and the carcinoma was then treated by extensive radiation therapy.

One must, however, be careful in the collection of these cases because in discussing the problem with Dr. Horner I find that he had also seen both of the cases reported above.

DR. F. H. FALLS.—I have seen three of these patients. The first was at Cook County Hospital in 1921. This patient entered the ward with a diagnosis of placenta previa. A living baby was delivered by cesarean section. The patient recovered and was sent to the tumor clinic for further treatment.

The second patient entered the clinic also as a case of placenta previa, for she had had severe painless bleeding about the seventh month. She was subsequently delivered at another hospital by cesarean section, at which time the carcinoma was

discovered. She re-entered our hospital for treatment of the carcinoma with radium and x-ray but did not respond favorably.

The third patient entered the clinic as an incomplete abortion. The right side of the cervix was extensively involved in a carcinomatous mass. I cauterized the carcinoma with a Percy cautery, and followed with radium and x-ray treatments. The patient was alive two years later.

If we are to make progress in the treatment of cancer of the cervix, we should not wait until bleeding begins before making a diagnosis. We should study the cervix of every pregnant woman for the possible presence of carcinomatous or precarcinomatous lesions. We should use the colposcope and paint every cervix with Lugol's solution at least once during the pregnancy, and certainly inspect and paint with Lugol's solution all patients in whom even slight bloody spotting occurs. Thus we may locate some of these tumors at a time when removal is still possible.

DR. DANFORTH (in closing).—The figures published by Dr. Baer are quite close to those that I found. One carcinoma in a hundred is complicated by pregnancy. His incidence of carcinoma in pregnancy, 1 in 10,000 does not vary much from what we found.

The single case of metastasis in the tissues of the child was the only one in the literature and was found in a French thesis published in 1873. We can assume that that is exceedingly rare. The papers which have appeared in the last thirty-five years indicate that in the opinion of most observers pregnancy does make carcinoma grow more rapidly.

Dr. Falls spoke about the use of the method of Schiller for early diagnosis. If it were possible during pregnancy, it would be very desirable. There is nothing in the literature which indicates that it has been tried. The discoloration of the cervix, which is part of the pregnancy picture, might interfere with the color contrast upon which the test depends. It would be an interesting thing to try, but I would be skeptical until I had tried it.

DR. FALLS.—I have done that within the last week. It shows up very beautifully.

THE EFFECT OF THE OVARIAN HORMONES ON THE HUMAN (NONPUERPERAL) UTERUS*

LEON KROHN, M.D., JULIUS E. LACKNER, M.D., AND SAMUEL SOSKIN, M.D., CHICAGO, ILL.

(From the Department of Gynecology and Obstetrics and the Department of Metabolism and Endocrinology of Michael Reese Hospital)

THE physiologic effects of the ovarian hormones on the uterus of the experimental animal have been well established. It is known that the estrogenic principle and progesterone are antagonistic in their effects on uterine motility. The estrogenic hormone enhances the rate and amplitude of uterine contractions,[1, 2] probably by sensitizing the uterine muscle to the oxytocic principle of the pituitary gland.[3, 4] Progesterone has been shown to decrease the activity of the uterus,[5-7] and to inhibit the normal response of the uterine muscle to the oxytocic principle of the posterior pituitary gland.[8]

*Read before the Chicago Gynecological Society, November 20, 1936.

The application of the above, and similar experimental observations on laboratory animals, to the treatment of the human patient in gynecologic practice is beset with many pitfalls. The repeatedly demonstrated species differences in the response of various laboratory animals to endocrine preparations cannot but engender misgivings in the mind of the conscientious gynecologist who is striving to apply these newer experimental findings on animals to the treatment of the ailments of the human female. It need hardly be emphasized that it behooves the science of gynecology to keep pace with the progress of endocrinology, by obtaining direct evidence of the applicability of the latter to the human subject, by the use of similar objective experimental methods.

In accordance with these considerations Moir[9] studied the motility of the puerperal human uterus by introducing a rubber bag connected by rubber tubing to a recording device. More recently, Falls and two of the present authors[10] have reported studies on the effects of estrogenic substance and of progesterone on the human puerperal uterus, using the method described by Moir. This work was consistent with previous reports of similar studies in laboratory animals and objectively confirmed our clinical impression that progesterone was of value in the treatment of threatened abortion through its inhibitory action on uterine contractions.[11] Lubin and Clarke[12] have since utilized this principle in treating afterpains with progesterone, in a large group of puerperal women, and have obtained relief in about 90 per cent of their cases.

In applying the above to the treatment of certain disorders in the nonpregnant and nonpuerperal woman, it seemed desirable to obtain experimental evidence as to whether or not the nonpregnant and nonpuerperal human uterus reacted identically with the puerperal organ. Partly because of the greater technical difficulties involved, few experimental studies on the motility of the human nonpregnant and nonpuerperal uterus have been made.

Moir[13] applied his method of recording contractions of the puerperal uterus on a miniature scale to the nonpuerperal uterus. He constructed a small rubber bag on the end of a hollow sound which could be introduced into the uterine cavity. He was able to record rhythmic contractions produced by the uterus by connecting the small uterine bag with a Hurthle manometer. These contractions were frequent, regular, and small during the first half of the menstrual cycle. After the sixteenth day they became increasingly stronger but less regular. He was able to produce a spasmodic contraction of the uterus with intramuscular injections of pituitary extract, irrespective of the stage of the menstrual cycle. These observations are contrary to those made by Knaus.[14] The latter used a similar method to study the response of the human uterus to intravenous injections of pituitary extract. He found that during the first fourteen days of the menstrual cycle the regular rhythmic contractions showed an increase in muscular tone forty to fifty seconds after the administration of pituitary extract. Knaus reported that after the sixteenth day, the uterus exhibits a decreased capacity for spontaneous contractions and becomes flaccid and sluggish with a completely negative pituitary reaction. This state continues until twenty-four hours before the onset of menstruation when

the uterus again behaves as it did during the first fourteen days of the cycle. He attributes the failure of response to pituitary extract during the last half of the cycle to the formation of the corpus luteum and liberation of the corpus luteum hormone. It was by this method that Knaus estimated the time of ovulation.

Falk and Nahon[15] obtained tracings of human uterine contractions by using a direct electrical "lead off" from the uterus through the electrocardiograph. They found a definite increase in activity from the ninth to the eighteenth day of the menstrual cycle. Repeated injections of theelin seemed to augment the waves irregularly.

We wish to report some observations on the effects of estrogenic substance* and of progesterone† on the human nonpregnant and nonpuerperal uterus, in normal women and in women suffering from certain endocrine disorders.

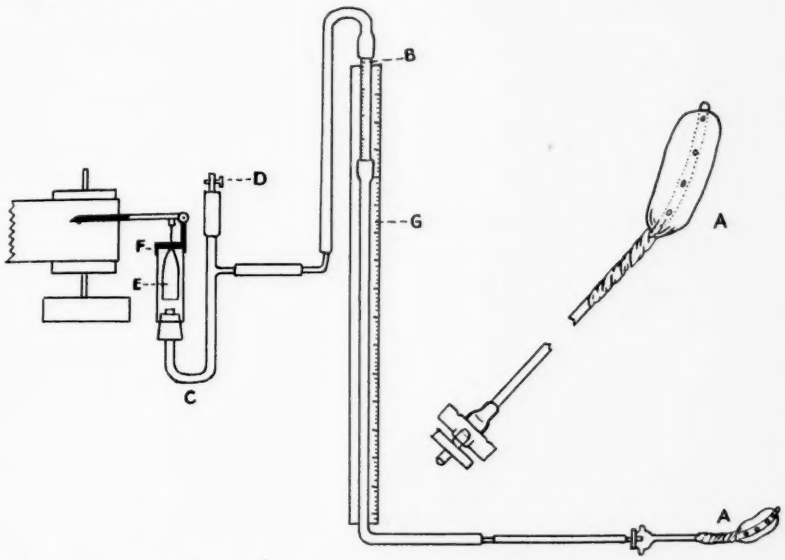

Fig. 1.—Apparatus for recording uterine motility at known volume and pressure. (*A*) Baloon ensemble, (*B*) calibrated leveling tube, (*C*) water manometer, (*D*) stopcock, (*E*) Balsa-wood float, (*F*) metal cap supporting the recording lever, and (*G*) movable scale.

PROCEDURE

In a small group of selected cases three modes of investigation were simultaneously followed at various intervals in the menstrual cycle of each subject. The motility of the uterus was quantitatively recorded, and on the same day that each tracing was made, endometrial biopsies were taken and blood and urine specimens were collected for determination of hormone content.

Uterine motility was recorded with the apparatus diagrammatically represented in Fig. 1. It consists essentially of a rubber balloon (*A*) for insertion into the uterus, a calibrated leveling tube (*B*), and a water manometer (*C*).

The balloon ensemble (*A*) is made from a metal uterine insufflation catheter the end of which is occluded by a rounded metal tip. The tip is held in place by

*Progynon B (Schering).
†Proluton (Schering).

a threaded projection which screws into a corresponding inside thread in the end of the catheter. A number of perforations are made along the wall of the catheter for a distance of 4 cm. from the tip. The balloon proper consists of a piece of penrose tubing, one end of which has been smoothly sealed. With the tip of the catheter removed, the penrose tubing is pulled over the end of the catheter. The metal tip is then screwed into place through a small perforation in the sealed end of the penrose tubing. The joint is made tight with rubber cement. The open end of the penrose tubing is then firmly closed around the body of the catheter, beyond the perforations, by the use of strips of thin rubber sheeting and rubber cement. The lumen of the catheter now communicates with the interior of a closed balloon by way of the perforations in the catheter wall. The catheter running through the balloon gives it the necessary rigidity for insertion into the uterus.

The method of recording the variations in volume and pressure of the rubber balloon was devised by one of us (S. S.) and has not been hitherto described. The leveling tube (*B*) consists of a straight 10 c.c. pipette, calibrated to tenths of a cubic centimeter from which the tip has been removed. The water manometer (*C*) consists of a narrow arm (8 mm. inside diameter glass tubing) which communicates through rubber pressure tubing with the leveling tube (*B*) on the one hand, and through the stopcock (*D*) to the air. On the short end of the narrow arm a wide glass tube (20 mm. inside diameter) is affixed by means of a rubber stopper. Into this wide tube is loosely fitted a balsa-wood float coated with celluloid (*E*). Wire pins circumferentially placed around the top and bottom of the float act as guides and prevent surface tension interference. The top of the wide glass tube carries a metal cap (*F*) from the side of which an upright projects. The tip of this upright serves as the fulcrum for a light recording lever.

To operate the apparatus, the balloon (*A*), catheter and connecting tubing up to the leveling tube (*B*) are filled with water and all air bubbles are eliminated. The manometer (*C*) is filled with water until the float (*E*) rides freely. The stopcock (*D*) is left open to the air. By raising the balloon (*A*) above the level of the leveling tube (*B*), it is caused to collapse as far as possible. A pinchcock is placed on the rubber tubing leading into the catheter. The balloon (previously sterilized) is now inserted into the uterus of the subject, and is held in place by an elastic band by which it is anchored to a single vulsellum placed in the anterior lip of the cervix. The movable scale (*G*) is adjusted so that its lowest point is at the level of the uterus. The level of the meniscus in the leveling tube (*B*) is noted. The pinchcock is removed from the rubber tubing leading to the balloon. The latter fills according to the capacity of the uterus. The position of the leveling tube (*B*) is now adjusted until the water meniscus within it is at the level of the point on the scale (*G*) which indicates the pressure at which it is desired to make the observations. The level of the meniscus in the leveling tube (*B*) is again noted. The difference between this and the previous reading (plus the volume of the intrauterine portion of the catheter and the balloon as a correction) gives the intrauterine capacity. The stopcock (*D*) is now closed, and the manometer begins to record uterine motility, at a known volume and pressure. To quantitate the records in cubic centimeters of volume change, the manometer is calibrated in the conventional manner.

The extraction of the blood for the estrogenic and gonadotropic hormones was made on a single specimen of blood according to the method described by Freed.[16] In this procedure acetone is used to precipitate the whole blood. The fat-soluble estrin remains in the supernatant acetone while the water-soluble gonadotropic hormone is easily extracted from the precipitated proteins by acidified 50 per cent alcohol.

The urine was extracted for estrogenic substance only, since it has been shown that the amount of gonadotropic hormone (prolan) in the urine parallels that in the blood.[17] The twenty-four-hour urine specimen was divided in two; one-half

was extracted by the tungstic acid precipitation method[18] for free estrin and the other half was extracted for total estrin by preliminary acid hydrolysis and subsequent tungstic acid precipitation.[19]

Castrated mice were used for the assay of blood estrin, the test being called positive if the extract from 40 c.c. of blood produced a cornified smear in one mouse in forty-eight to sixty hours, signifying at least 25 M.U. per liter. The gonadotropic hormone was assayed on infantile rats, the test being called positive if the extract from 40 c.c. of blood produced an Aschheim-Zondek reaction in twenty-three- to twenty-five-day-old rats in one hundred hours.

The urinary estrin was assayed on castrated mice, also. Since there seems to be considerable variation in the actual amount of estrin corresponding to a mouse unit, depending on the strain of mice and the technique of assay, we have converted our mouse units into International Units. In our laboratory one mouse unit equals three International Units.

The endometrial biopsies were obtained with Novak's suction curette.[20]

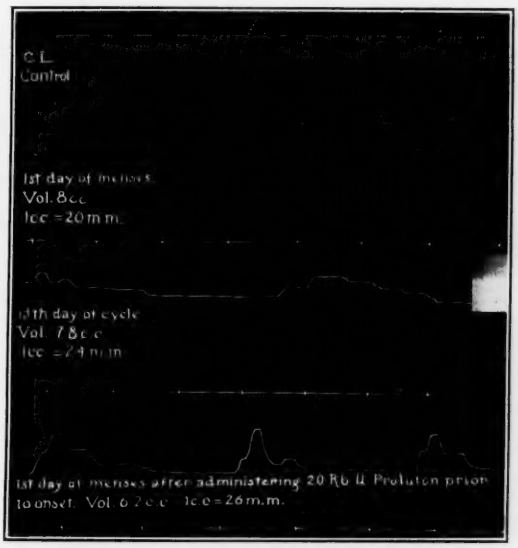
C. L.
Control
1st day of menses
Vol. 8 c.c.
1 c.c. = 20 m.m.
14th day of cycle
Vol. 7.8 c.c.
1 c.c. = 24 m.m.
1st day of menses after administering 20 Rb U Proluton prior
to onset. Vol. 6.2 c.c. 1 c.c. = 26 m.m.

Fig. 2.—Uterine motility in a normal control, before and after the administration of progesterone. (Photographic reduction 4½ times.) Recording pressure 100 cm. of water.

The following group of selected cases was studied. Illustrative graphic records are presented for each case (Figs. 2 to 6) and the results are summarized for purposes of comparison in Table I.

CASE 1.—(Normal Control, Fig. 2.) C. L., aged twenty-one years, para ii, gravida ii. No complaints, menstrual history normal, normal genital status, no previous operations. Studies were made on the first and fifteenth days of the menstrual cycle and on the first day of menstruation following the intramuscular administration of 5 European rabbit units of progesterone* given daily for four consecutive days prior to the onset of menstruation.

CASE 2.—(Normal Control, Fig. 3.) M. G., aged twenty-three years, para i, gravida i. No complaints, menstrual history normal, no previous operations, normal genital status. Studies were made on the first and fourteenth days of the menstrual

*Proluton (Schering).

cycle and on the first day of menstruation following the intramuscular injection of 10,000 International Units of estrogenic substance* given daily for five consecutive days prior to the onset of menstruation.

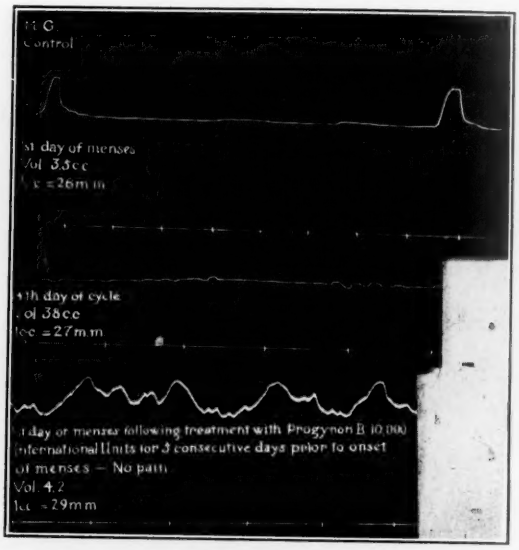
H. G.
Control
1st day of menses
Vol. 3.5cc
1cc = 26m m
9th day of cycle
Vol. 3.8cc
1cc = 27m m
1st day of menses following treatment with Progynon B 10,000
International Units for 5 consecutive days prior to onset
of menses — No pain
Vol. 4.2
1cc = 29m m

Fig. 3.—Uterine motility in a normal control, before and after the administration of estrogenic substance. (Photographic reduction 4½ times.) Recording pressure 100 cm. of water.

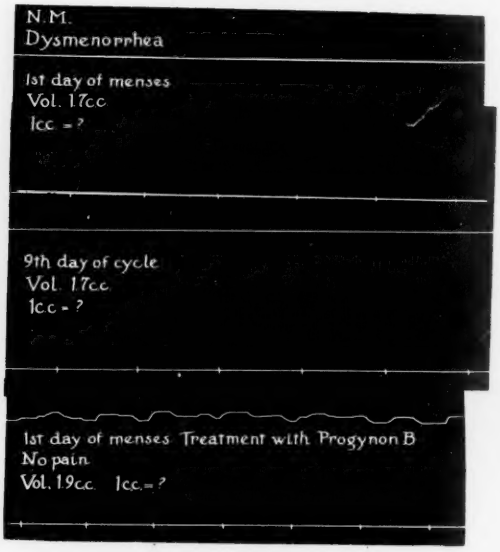

Fig. 4.—Uterine motility in patient with oligomenorrhea and dysmenorrhea following bilateral resection of ovaries, before and after treatment with estrogenic substance. (Photographic reduction 3½ times.) Recording pressure 100 cm. of water.

CASE 3.—(Oligomenorrhea and Dysmenorrhea, Fig. 4.) N. M., aged twenty-nine years, para 0, gravida 0. Dysmenorrhea and oligomenorrhea following bilateral resection of polycystic ovaries three years ago for amenorrhea. Uterus small and movable. No palpable adnexal pathology. Studies made on the first and ninth

days of the menstrual cycle and on the first day of menstruation following intramuscular injections of 10,000 International Units of estrogenic substance* three times a week for one month prior to the onset of menstruation.

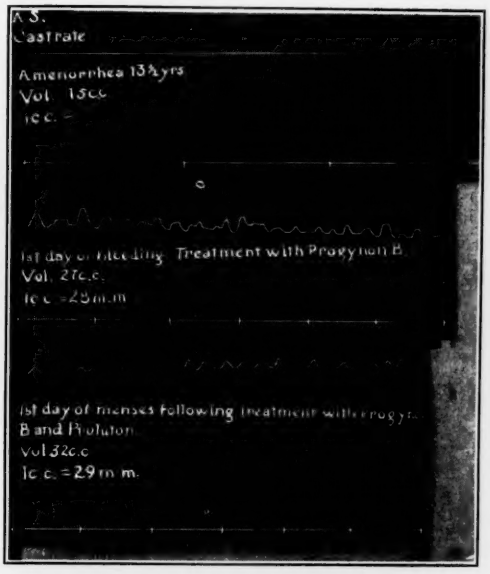

Fig. 5.—Uterine motility in a castrate, before and after treatment with estrogenic substance alone, and with estrogenic substance plus progesterone. (Photographic reduction 4 times.) Recording pressure 100 cm. of water.

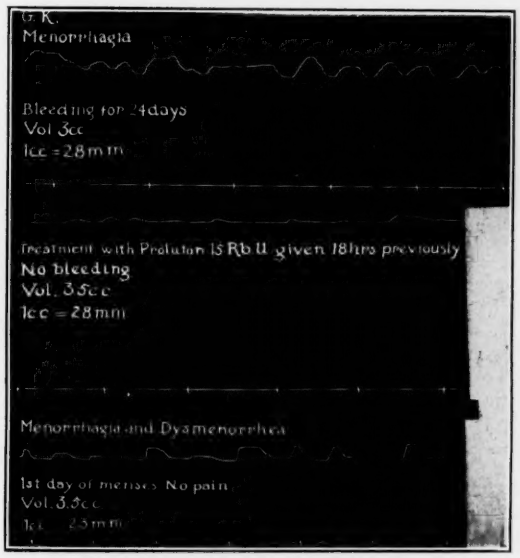

Fig. 6.—Uterine motility in patient with menorrhagia and dysmenorrhea, before and after treatment with progesterone. (Photographic reduction 4 times.) Recording pressure 100 cm. of water.

CASE 4.—(Castrate, Fig. 5.) A. S., aged thirty-one years, para 0, gravida i. Spontaneous miscarriage in 1921. Bilateral salpingo-oophorectomy fourteen years ago

TABLE I

CASE	AGE	PARA	MENSES	DIAGNOSIS	DAY OF CYCLE	HORMONE ADMINISTERED	UTERINE MOTILITY	UTERINE VOLUME	BLOOD		URINE ESTRIN	ENDOMETRIUM
									PROLAN	ESTRIN		
1 C. L.	21	ii	Normal	Normal	1st day of menses	None	Extremely large contractions. Regular, 1 every 2 minutes	8 c.c.	+	0	Free 30 Total 120	Cervical epithelium and glands
					15th	None	Moderate contractions Irregular in size and frequency	7.8 c.c.	0	0	Free <30 Total <30	Proliferating
					1st day of menses	Proluton 20 Rb.U.	Moderate contractions Regular, 1 every 2 minutes	6.2 c.c.	0	0	Free 30 Total 30	Early secretory
2 M. G.	23	i	Normal	Normal	1st day of menses	None	Moderate contractions Regular, 1 every 5 minutes	3.5 c.c.	0	0	Free 30 Total 30	Secretory
					14th	None	Small contractions Irregular	3.8 c.c.	0	0	Free <30 Total 60	Proliferating
					1st day of menses	Progynon B 50,000 I.U.	Moderately large contractions. Regular, 2 to 3 per minute	4.2 c.c.	0	0	Free <30 Total <30	Secretory
3 N. M.	29	0	Dysmenorrhea Oligomenorrhea Flow scant Lasts 2 days	Dysmenorrhea Oligomenorrhea	1st day of menses	None	No contractions	1.7 c.c.	0	0	Free 60 Total 60	Specimen insufficient
					9th	None	No contractions	1.7 c.c.				Specimen insufficient
					1st day of menses	Progynon B 100,000 I.U.	Small irregular contractions—1 to 2 per minute	1.9 c.c.	0	++	Free 20 Total 180	Late proliferating

TABLE I—CONT'D

CASE	AGE	PARA	MENSES	DIAGNOSIS	DAY OF CYCLE	HORMONE ADMINISTERED	UTERINE MOTILITY	UTERINE VOLUME	BLOOD		URINE ESTRIN	ENDOMETRIUM
									PROLAN	ESTRIN		
4 A. S.	31	0	Amenorrhea 14 yr.	Castrate Had bilateral salpingo-oophorectomy 14 yr. ago	L.M.P. 14 yr. ago	None	No contractions	1.5 c.c.	+	0	Free <30 Total 30	Specimen insufficient
					1st day of bleeding	Progynon B 90,000 I.U.	Small contractions Regular, 4 per minute	2.7 c.c.	0	0	Free 30 Total 30	Cervical epithelium and glands
					1st day of bleeding	Progynon B 90,000 I.U. Proluton 5 Rb.U.	Small contractions Regular, 4 per minute	3.2 c.c.	0	0	Free <30 Total <30	Hyperplastic endometrium
5 G. K.	25	0	Profuse 7-21 days	Menorrhagia	Flowing for 24 days	None	Moderate contractions Fairly regular, 2 per minute	3.0 c.c.	0	0		Proliferative
					25th day Flow ceased today	Proluton 15 Rb.U.	Very small contractions Fairly regular, 1 per minute	3.5 c.c.			Free 45 Total 90	Late proliferative
					1st day of menses	None	Small contractions Fairly regular, 2 per minute	3.5 c.c.	0	0	Free 30 Total 30	Proliferative

followed by amenorrhea. Uterus atrophic. No palpable adnexa. Studies were made before therapy was instituted, on the first day of bleeding following intramuscular injections of 10,000 International Units of estrogenic substance* three times a week for three weeks, and on the first day of bleeding produced by a similar course of estrogenic substance* which was followed by one injection of five European rabbit units of progesterone,† twenty-four hours later.

CASE 5.—(Functional Menorrhagia and Dysmenorrhea, Fig. 6.) G. K., aged twenty-five years, para 0, gravida 1. Spontaneous miscarriage at six and one-half months in February, 1935. Appendectomy in 1928. Menses profuse since onset lasting seven to twenty-one days with pain on first day. First studies made while patient was flowing and had been bleeding for twenty-four days. Was then given fifteen European rabbit units of progesterone.‡ The bleeding stopped eighteen hours later and the studies were repeated. Two months later similar observations were made on the first day of a normal menstruation.

DISCUSSION OF RESULTS (TABLE 1)

There is a wide range in the motility of the uterus of normal patients at corresponding times of the menstrual cycle. The uterus is usually quiescent during the midperiod, but the motility at this time may vary in normal patients from no contractions to moderate sized contractions. The maximum motility is on the first day of menstruation. The strength of the contractions seems to be in direct proportion to the size and volume of the uterus in women with a normal hormonal balance. Thus, in Case 1 (Fig. 2), the volume of the uterus was large and the contractions on the first day of menstruation were very intense, although the patient suffered no discomfort whatsoever. This patient was selected to demonstrate the inhibitory action of progesterone because of the large size of these contractions. At the subsequent period after the administration of twenty European rabbit units of progesterone, the contractions were less than one-third of their former size.

The volume of the uterus in Case 2 (Fig. 3) was relatively small. The contractions on the first day of menstruation were only moderate in size but after the administration of 50,000 International Units of estrogenic substance they were markedly increased both in intensity and frequency.

These two cases offer an excellent contrast between the actions of the two ovarian hormones in normal women. They demonstrate that the normal human nonpregnant and nonpuerperal uterus reacts to these hormones in a manner similar to the response of the human puerperal uterus, and of the uterus of laboratory animals.

Case 3 (Fig. 4) presents a typical example of a deficiency of the estrogenic principle. The uterus was small and the patient's menses were scant and painful. No spontaneous motility could be demonstrated either at the mid-period or on the first day of menses. However, after

*Progynon B (Schering).
†Proluton (Schering).
‡Proluton B (Schering).

intensive therapy with estrogenic substance, small, irregular contractions appeared. This was associated with a strongly positive estrin determination in the blood and a marked increase of estrin in the urine. The menstrual period increased from two to five days and the quantity was more profuse. There was no pain accompanying this period.

In the case of the castrated woman (Case 4, Fig. 5) the uterus was atrophic and no motility could be demonstrated. Intensive treatment with estrogenic substance produced an artificial bleeding and small rhythmic contractions. Therapy with estrogenic substance and progesterone also produced an artificial bleeding with small contractions of the uterus. The atrophic endometrium became hyperplastic. The volume of the uterus approximately doubled.

The case of functional menorrhagia (Case 5, Fig. 6) is an example of a deficiency of progesterone. A uterine hemorrhage of twenty-four days' duration was stopped in eighteen hours with fifteen European rabbit units of progesterone. This therapy also produced a decrease in the motility of the uterus. The endometrium changed from a proliferative to a late proliferative type.

The results of the administration of estrogenic substance or progesterone to the latter three patients indicate that the use of the appropriate hormone as substitutional therapy in women suffering from endocrine deficiencies is a rational attempt to bring about a temporary return toward the normal physiologic and clinical state.

CONCLUSIONS

1. A method for recording the motility of the human nonpuerperal and nonpregnant uterus is described.

2. The method is harmless and is of value in the study of endocrine disorders of the female.

3. The normal human uterus is quiescent at the mid-period and its motility is greatest at the onset of the menstrual period.

4. Estrogenic substance augments the motility of the normal human nonpregnant and nonpuerperal uterus; progesterone decreases the motility.

5. Estrogenic substance induced motility and initiated bleeding in the uterus of a woman castrated fourteen years previously. It induced motility, increased menstruation, and relieved dysmenorrhea in a woman with bilaterally resected ovaries. Progesterone decreased the motility and stopped the bleeding in a woman suffering from functional menorrhagia.

We are indebted to the Schering Corporation for ample supplies of progynon B and proluton; to Dr. Otto Saphir for generous cooperation with the histologic interpretations; and to Dr. S. Charles Freed for the performance of the arduous task of assaying many samples of blood and urine for their hormone content.

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DISCUSSION

DR. FRED H. FALLS.—The importance of this paper lies in the fact that the observations made were recorded by instruments of precision and could not have been influenced by any bias which the investigators may have had toward the results of the experiments. This puts the use of these hormones on a rational basis.

When one injects the estrogenic hormone or progesterone different physiologic reactions can be noted and measured. However, as these investigators have pointed out, one has to be careful in the interpretation of the phenomena observed, since certain reactions might conceivably be the result of coincidence. For instance, in the case of bleeding which was produced in the uterus years after a castration, one would like to know how many times was this woman made to bleed? Were subsequent injections successful or not? How long was this patient observed? How many cases of each type were treated successfully? Were some cases encountered which did not respond at all to injections?

In our experience, the most striking effect of the use of progesterone has been in controlling menorrhagia and metrorrhagia occurring in young girls shortly after menstruation begins. We have had two cases which responded favorably to progesterone after follutein had been tried and had proved only temporarily efficacious. We have had one patient with a severe purpura hemorrhagica, in whom various forms of endocrine therapy had been used unsuccessfully, before progesterone produced a definite effect.

The tracings here presented are far better than those of Knaus, whose contraction curves were very small. We have found that by using a water manometer instead of a mercury manometer, we were able to get very delicate tracings of the effect of pitressin on the large bowel, using the method of Moir, with the bag inserted in the rectum.

Another important point is that the data here presented relate to the effects of these substances on the human uterus and are, therefore, not analogies drawn from observations made on animals.

DR. S. SOSKIN.—It is true that the contractions of a large uterus can be recorded with a less elaborate manometer than we used. Our apparatus, however, records the motility of a small, nonpuerperal uterus with equal facility, and yields more quantitative data, since it operates at a known volume and at a constant known pressure.

Other interesting aspects of this work are the great variability in the estrin and prolan of blood and urine in normal individuals, and the poor correlation between these hormone contents and the clinical manifestations in patients suffering from endocrine dysfunctions. To those of us who have been looking forward to hormone-testing as an aid to clinical practice, this seems rather disappointing. But perhaps we can comfort ourselves by ascribing this apparent lack of correlation to the inadequacy of our present knowledge. In this regard you may be interested to know that Dr. Freed, of my department, and I are just reporting on the probable presence of at least four factors in the ovary, other than estrin or progesterone, which have to do with the menstrual cycle. There is apparently an inhibitory substance, an augmenting substance, a factor concerned with endometrial rhythm, and also a factor influencing breast development. When we have learned to test for such factors, in addition to those which we can now assay, we may then be in a better position to interpret the clinical status of our patients in quantitative hormonal terms.

DR. KROHN (in closing).—We attempted to emphasize the fact that the effects produced with the ovarian hormones were temporary in nature because the type of therapy was substitutional. We have made approximately eighty similar studies and have been able frequently to reproduce the results obtained in this selected group of cases.

Encouraging results are obtained with cases of functional menorrhagia when large doses of progesterone are administered (15 to 20 International Units). Unfortunately, there are some patients who do not respond to this form of therapy. It has been recently recommended that more satisfactory results are obtained with smaller doses of progesterone if a preliminary dilatation and curettage is done.

We were unable to confirm the observation made by Moir, of the disappearance of the arterial pulsations at the peak of the contractions obtained from a patient suffering with dysmenorrhea. In a recent study of a group of dysmenorrheic patients, we frequently observed these pulsations continuing throughout the peak of the contractions. We, therefore, cannot agree with the suggestion that pain in primary dysmenorrhea is due to an ischemia of the uterus.

Lundquist, B., and Runström, G.: Hysterosalpingography, Acta obst. et gynec. Scandinav. **16**: 415, 1936.

After discussing the literature on hysterosalpingography, the authors present their own material, which embraces 55 cases. Fifty-one of these were examined on account of sterility, and 4 for other reasons. They report, in addition, a case where radiograms placed at their disposal illustrate injection into the venous system. In the experience of the authors, the method is extremely valuable. With strict indications and correct technical application it entails very little risk and gives valuable information. In no less than 25 per cent of the normal cases (28), the method proved curative, pregnancy having followed within a few months.

In order, however, to make the method wholly effective diagnostically, the authors perfected their roentgen technique so that, in cases where pathologic changes of the pelvic organs are visible, the roentgen examination is made with the patient in different positions using in addition to the dorsal, the lateral, upright, and upside-down positions. The effect of this procedure has been very satisfactory.

J. P. GREENHILL.

PYELOURETERITIS IN PREGNANCY*

Etiology, Acute Phase and Treatment

Herbert F. Traut, M.D., New York, N. Y.

(From the Department of Obstetrics and Gynecology, New York Hospital and Cornell Medical College)

PYELITIS as a complicating disease of pregnancy has been recognized and treated for many years, but despite this fact it has been one of the least understood of the obstetric diseases. It is difficult to explain why this should have been so. However, it should be true no longer, for recently much new light has been shed upon the physiology of the ureter in pregnancy and the etiology of pyelitis, on the one hand; while on the other, diagnostic methods and the treatment of the disease have been improved, and we have gained an understanding of the sequelae of pyelitis in the woman and her offspring. This new information has necessitated a complete revision of our ideas concerning the significance of pyelitis in pregnancy, with the result that whereas formerly we were inclined to classify it as one of the minor complications, we are now forced to consider it among the more important. Many of the data which have brought about this change in point of view have been obtained by means of improved methods of urologic diagnosis. More important, however, has been the accumulated information which has resulted from cooperation between urologists and obstetricians in obstetrical hospitals both in this country and abroad. We shall attempt to present the subject of pyelitis as a complicating disease of pregnancy and the puerperium in the light of the more recent developments.

As some confusion has been occasioned by differences in terminology, it may be well at the outset to indicate what is meant by some of the commoner terms in this field. As the name indicates, pyelitis is an inflammatory disease affecting the pelvis of the kidney. However, when the renal pelvis is inflamed the ureter is usually involved as well; hence it is more accurate to use the term pyeloureteritis instead of pyelitis. If the infection extends from the renal pelvis into the parenchyma so as to involve the ducts and secretory elements of the kidney, one speaks of pyelonephritis. In addition, other terms are used to indicate more advanced stages of the inflammatory process: pyonephrosis indicates a marked dilatation of the renal pelvis and abdominal ureter associated with a purulent inflammation. In distinction, one speaks of hydronephrosis and hydroureter when there is marked dilatation of the renal pelvis or ureter without inflammatory involvement being present (Fig. 1).

*Read at a meeting of the New York Obstetrical Society, January 12, 1937.

The incidence of pyeloureteritis as a complication of pregnancy is such as to rank it in importance with chronic nephritis and cardiac disease. Our experience at the New York Lying-In Hospital in 15,000 consecutive deliveries gives the following comparison:

	PER CENT
Pyelitis	2.02
Chronic nephritis	2.29
Cardiac disease	3.66

Not only does pyeloureteritis rank with chronic nephritis and cardiac disease in frequency but if neglected, the sequelae may also cause it to rank in importance with these diseases because of the impairment of

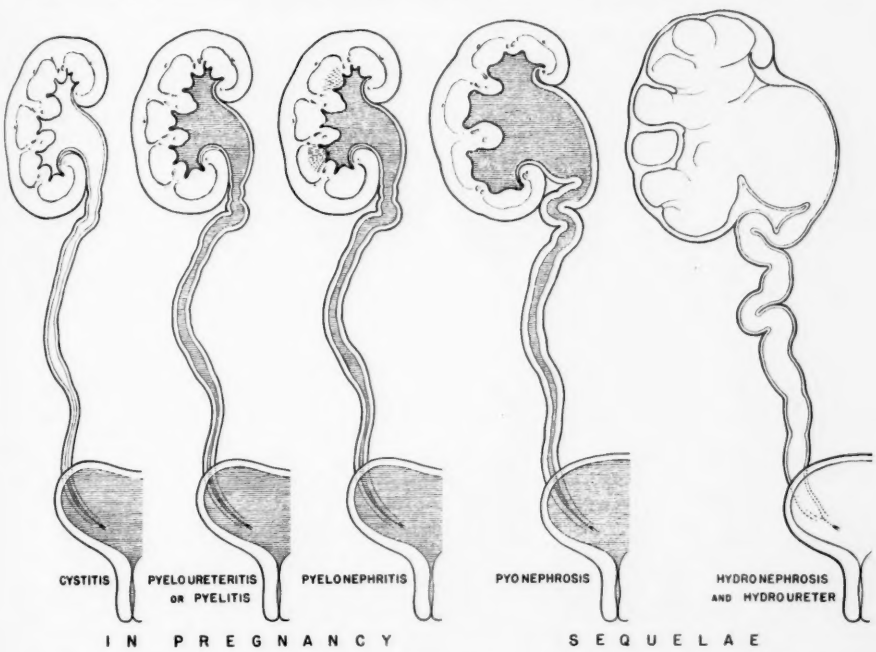

Fig. 1.—A diagrammatic demonstration of the portions of the urinary tract involved in the common types of infection complicating pregnancy and their sequelae in the puerperium. The shaded portions represent the extent of the infection.

health it may cause to mother and child. On the other hand, when adequately treated, the disease can be influenced to such a marked degree that most of its harmful effects can be obviated. It is, therefore, of primary importance that all obstetricians should have a clear understanding of the nature of the disease and its treatment.

ETIOLOGY

Three factors are of paramount importance in the etiology of pyeloureteritis of pregnancy. These are stasis, trauma, and infection.

Unfortunately a moderate degree of stasis of urine in the renal pelvis and ureter is a physiologic characteristic of pregnancy. In about 80

per cent of all women, x-ray photographs made during the seventh and eighth months of pregnancy disclose a dilatation of the ureter and kidney pelvis. This hydronephrosis and hydroureter are unmistakable evidences of stasis of urine. We may say, therefore, that 80 per cent of all pregnant women are predisposed to pyeloureteritis in the sense that they are always possessed of one of the important etiologic factors of the disease.

It is also significant that this stasis of urine is much more frequent and more marked on the right side than on the left, and furthermore, that with corresponding frequency the infection of the upper tract is on the right side rather than the left. As a result of the recent investigative work done in this field, we are enabled to make definite statements regarding the causes of urinary stasis in pregnancy. Most fundamental of these is muscular atony. It has been shown that the smooth muscula-

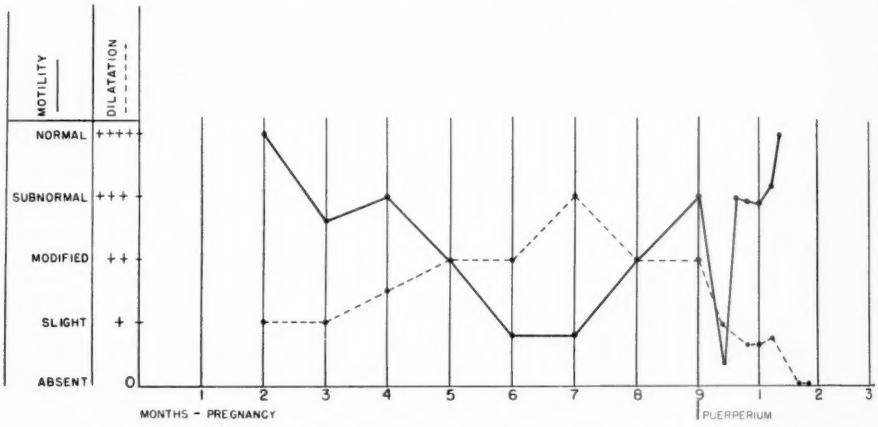

Fig. 2.—A composite graph made from the data obtained from the study of fourteen normal pregnant women. The solid black line shows the variations in the peristaltic activity of the tract with reference to the duration of pregnancy and the puerperium. The interrupted line shows the degree of dilatation of the tract. It will be seen that in general they are inversely proportional, very strongly suggesting a causal relationship.

ture of the ureter responds to the influences of pregnancy in a manner very similar to that of the uterus. To be specific, the smooth muscle coats of the ureter lose much of their irritability from the third to the ninth months of pregnancy (Fig. 2). This means reduced contractility and loss of peristaltic activity, with the result that when the weight of the enlarging uterus encroaches upon the already atonic ureter, there is increased difficulty in discharging urine into the bladder. The urine, therefore, accumulates and distends the flaccid ureter and kidney pelvis, producing the hydroureter of pregnancy. In addition, the pregnant uterus usually rotates on its long axis toward the right. In doing so, it brings greater pressure to bear upon the right ureter than upon the left, which in turn produces more marked stasis and ureteral dilatation in

the right tract than in the left. This, it is thought, accounts in a large measure for the predominance of right-sided urinary infections in pregnancy.

The second etiologic factor of prime importance is infection, which results when a sufficient number of pathogenic microorganisms are introduced into the upper urinary tract to bring about inflammation.

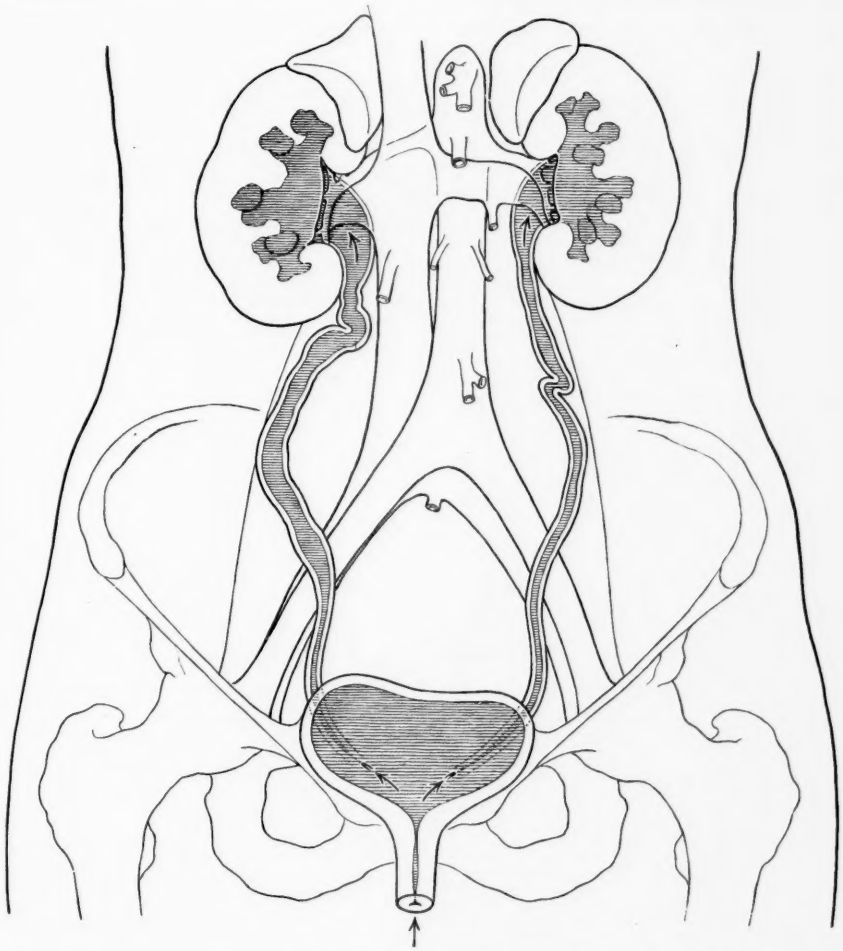

Fig. 3.—This picture shows the dilatation of the ureter and renal pelvis together with the lateral displacement and tortuosity of the ureter which comprise the characteristic changes in the tract due to pregnancy, the so-called physiologic hydroureter of pregnancy. The arrows and shaded portions demonstrate the "ascending infection" theory of the etiology of pyelitis, which is no longer accepted.

The phrase, "a sufficient number of microorganisms" has been used advisedly, for it has been demonstrated that a mild bacteriuria can exist without producing any considerable inflammatory reaction. It is noteworthy and probably very significant that over 95 per cent of the cases of pyelitis of pregnancy are caused by organisms belonging to

the colon group of bacilli. Occasionally we encounter streptococcus, staphylococcus, or proteus infections, but these are in the small minority. The fact that *B. coli* is the chief pathogenic invader suggests very strongly that this organism comes to the urinary tract from the bowel and that it does this either by direct ascent of the lumen of the tract or is transported there by way of the lymphatic system. The

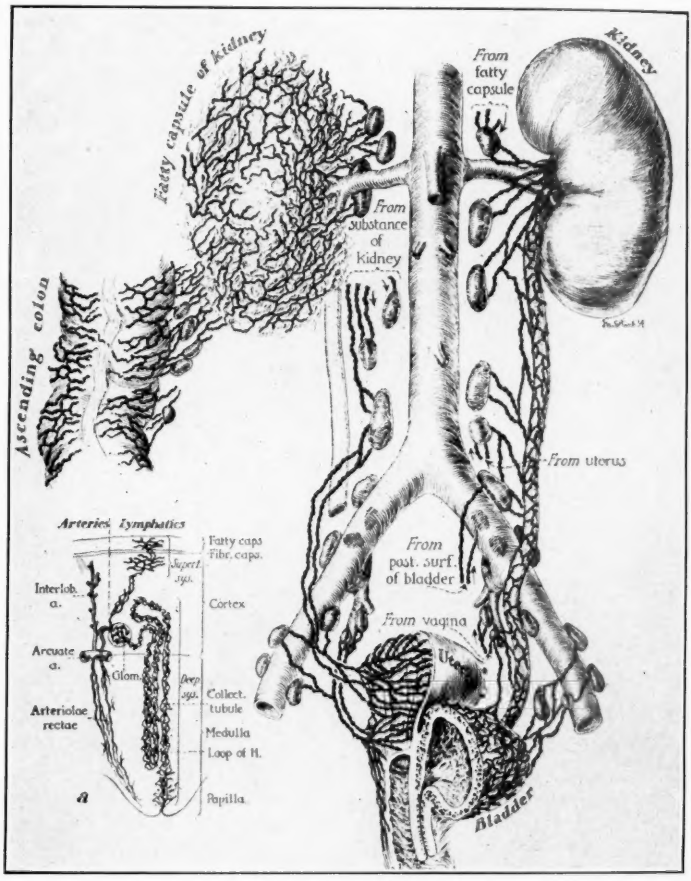

Fig. 4.—The various lymphatic pathways by which infectious organisms may reach the kidney and ureter from the large bowel and the pelvic organs. (H. A. Reimann.) (Permission of Lea & Febiger.)

older concepts of the mode of infection emphasized direct extension from the perineum to the urethra, thence to the bladder, and finally into the ureters and kidney pelvis (Fig. 3). This in times past has seemed a very reasonable hypothesis; however, most of the recent investigative work tends to indicate that this is not a common route. As Franke and others have shown, it now appears much more likely that in many instances the colon organisms are transmitted from the large bowel to

the capsule of the right kidney by the lymphatic system. This offers another explanation for the predominance of right-sided infections. Another very important route of infection also involving the lymph stream is that which drains the pelvic organs, particularly the cervix, vagina and urethra, and extends upward along the course of the ureter to the region of the renal pelvis where it empties into the lateral channels communicating directly with the thoracic duct. The studies of Winsbury-White have given such convincing proof of this lymphatic drainage that one is inclined to believe that this may be the most important of all routes of infection (Fig. 4).

Blood stream infection is in all probability secondary to that of the lymphatic system. In the majority of cases it would seem to play a minor part, despite the fact that there are competent observers who express themselves to the contrary.

The third etiologic factor is trauma. Scott has shown conclusively that the simple passage of a urethral catheter in the male may cause enough excoriation of the mucous membranes to permit large numbers of microorganisms to gain entrance to the blood stream and produce the well-known "catheter fever." Whether the bacteria reach the blood stream directly or by way of the lymph stream is a mooted point; the fact remains that slight trauma may cause the dissemination of the pathogenic organisms. Certainly the trauma of delivery together with the secondary atony of the ureter which occurs immediately after childbirth are the principal factors in causing postpartum pyelitis.

PATHOLOGY OF PYELOURETERITIS

In the acute phase of the disease the infectious agent, usually *B. coli* in one of its many forms, produces an inflammation of the internal aspects of the ureter and kidney pelvis, with swelling and edema accompanied by an outpouring of leucocytes to form an exudate on the surface mucosa. Flakes of the leucocytic exudate become detached, float in the urine, and thus produce the cloudy urine which, when observed under the microscope, is seen to contain the "clumped pus cells" so pathognomonic of pyeloureteritis.

Later the submucosa and muscular layers become involved with all the concomitants of an extensive inflammatory reaction. In the early stages of an acute attack the tissue response is largely made up of tissue fluids and leucocytes. However, when prolonged, the connective tissue elements appear and become organized into structures, which at first are loosely arranged, but later consolidate to form fibrosis. The longer the process is allowed to progress, the more its density is increased, with the result that the muscular portions of the ureter and kidney pelvis may

become so rigidly fixed in scar tissue as to render them incapable of peristaltic action, even after the inflammation has subsided. Thus the end-result may be a partially or completely inactive kidney pelvis and ureter, or if the process be continued longer, the woman may be left with a permanent pyo- or hydronephrosis. An appreciation of this sequence of pathologic developments impresses the necessity for the early employment of those therapeutic procedures which obviate or minimize them. Even with the best treatment we now know, we cannot completely stop the pathologic changes during pregnancy, for we have not yet learned how to rid the tract of infection while the uterus is distended by the fetus. Even though the patient becomes afebrile and the other symptoms subside, the urine cultures continue positive, as a rule, until some time after delivery, which means that a smouldering infection

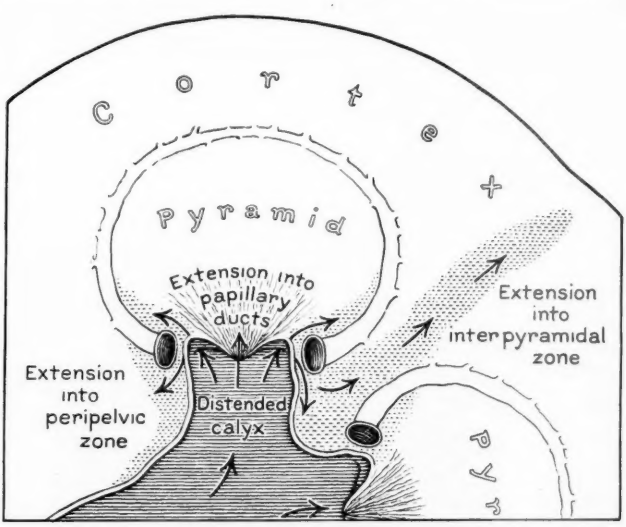

Fig. 5.—A demonstration of how infection may spread to the renal cortex from the kidney pelvis producing pyelonephritis by direct extension.

persists which, at any time, may cause a recrudescence of the acute aspects of the syndrome. The low grade infection of the tract progressively adds to the fibrosis of the ureters. However, this is small in amount as compared to the damage done during the acute exacerbations. Hence, a great deal can be accomplished by employing those forms of treatment which keep the reaction in a quiescent state.

The most serious form which the infection may assume is an extension upward from the renal pelvis into the glandular portions of the kidney, either by direct extension through the foramina papillaria or by extension into the peripelvic space and thence into the region of the interpyramidal septa (Fig. 5). Pyelonephritis is serious, either because it may markedly reduce the excretory function of the kidney or, because of its intimate relationship to an extensive vascular bed, it may produce such a

widespread infection as to endanger the life of the patient. It is quite probable that a slight degree of pyelonephritis occurs more frequently than is commonly thought, for it is very difficult to make a clinical differentiation between pyeloureteritis and pyelonephritis. Indeed, one cannot make a differential diagnosis until the inflammation has involved a considerable part of the kidney, so that its secretory activity is impaired and there is retention of nitrogenous substances in the blood stream. When the kidney is thus handicapped, one can easily come to the correct conclusion by examining the blood for nonprotein nitrogen constituents. When these are increased in amount, there is marked inflammation of the renal cortex, and when normal, there is little or no such extension. It goes without saying that a markedly elevated nonprotein nitrogen content of the blood indicates a very serious involvement of the kidney which demands vigorous and prompt measures if the patient is to be saved. More will be said concerning pyelonephritis when the treatment of the disease is considered.

CLINICAL FEATURES OF THE DISEASE

In our experience, pyeloureteritis occurs as frequently in multiparas as in primigravidas. The onset of the initial attack is usually in the last trimester of pregnancy or in the early puerperium. Not infrequently, however, we see women who, having had pyelitis in a previous pregnancy, afterward exhibit an exacerbation in the form of an acute reaction in the first or second trimester of a succeeding pregnancy.

The first symptom may be hematuria, although this is by no means constant. The acute phase is usually accompanied by a marked elevation of temperature, hectic in type, and associated with chills. Anorexia, nausea and vomiting and some abdominal distention are frequently seen. There is usually pain, or at least demonstrable tenderness in the costovertebral angle corresponding to the side of the affected kidney. Upon inspiration, exquisite tenderness of the descending kidney may be elicited by deep palpation of the flank.

A catheterized specimen of bladder urine will usually show definite bacilluria and pyuria, the pus cells being clumped together, while bacteriologic culture of the specimen will reveal a strain of the colon family of organisms in the great majority of patients. Urine culture is important as staphylococcus, streptococcus, and *B. proteus* infections do not respond satisfactorily, as a rule, to the same treatment that is used for the colon organisms. Anemia is a frequent part of the picture because of the hemolytic propensities of many of the colon organisms. Blood cultures taken at the height of a chill are occasionally positive, indicating that the organisms have gained access to the blood stream. However, such cultures are much more commonly negative.

Usually the febrile phase of the disease is a short one when well treated, passing into a subacute condition after a period of four or five days. A remission may occur at any time, for as has been pointed out, the infection is rarely cured during pregnancy; it becomes quiescent but is an ever present source of danger.

The infection is found to involve the right tract in the great majority of patients. This is so true that should the infection seem to be on the left side, one should at once think of the possibility of a bilateral infection and take the steps necessary to determine whether or not this be true. The importance of bilateral infections as compared to those which are definitely unilateral cannot be overemphasized, because the hazard to the patient is not merely doubled, but, on the contrary, is increased many times.

TREATMENT

The treatment of pyeloureteritis should be varied according to several factors which must be taken into consideration before deciding upon the course to be followed. Is the patient in the early stages of pregnancy, or is she approximately at term? What has been her previous obstetrical and urological history? Is the infection unilateral or bilateral? Is there adequate renal function or has the infection already reduced excretory activity? These are a few of the more important questions that must be answered.

Generally speaking, the treatment of the disease falls into two general categories; the first, which applies to the vast majority of patients, may be considered conservative or palliative, and the second, radical.

The palliative treatment consists of rest in bed with frequent change of position which shifts the weight of the uterus from side to side, so that the ureters can be emptied more readily, thus improving drainage of the tract. Fluids are forced, a bland diet is prescribed and a mild saline purge administered every other day. Immediately upon admission, three laboratory procedures are carried out: (1) A catheterized bladder specimen is secured for examination and culture. (2) The blood is examined to discover whether or not there is nitrogen retention. (3) An intravenous x-ray pyelogram is made to furnish information as to the degree of damage already sustained by the inflammatory process and to serve as a rough test of kidney function.

If the organism is a colon bacillus, *if* there is no nonprotein nitrogen retention, and *if* the process is unilateral, the patient is carried on the palliative treatment for as long as seven days. Usually before that time has elapsed there will be a marked fall in temperature, and the kidney tenderness will be greatly diminished. In fact, most patients will respond to this treatment and go on to term satisfactorily. After the temperature has been normal for several days the patient is allowed to resume her activities in a modified manner, emphasis being placed upon

frequent rest periods in the recumbent position during the day, and a continuation of an augmented fluid intake amounting to 3,000 c.c. per day. Close observation of the patient is maintained because of the danger of remission.

If, on the other hand, the patient does not respond to this conservative treatment after six or seven days of palliative therapy, the affected ureter is catheterized with a No. 7 or No. 9 catheter which is left in place with the tip high in the tract to provide drainage. The catheter is left in position not more than three or four days when it is removed whether or not the temperature and other symptoms have subsided. Frequently the desired response will come twenty-four or forty-eight hours after removal of the catheter. While the catheter is in position, lavage of the kidney pelvis with normal saline solution is carried out at four-hour intervals.

When the infection is bilateral, one is not justified in as long a period of palliation, particularly if the patient is two or three months from term. The possibility of pyelonephritis with suppression of function is so greatly increased that, if the patient does not respond promptly to palliative treatment or the use of the indwelling catheter, the uterus should be emptied. If, in addition to a well-established bilateral infection, one discovers nonprotein nitrogen retention, the termination of pregnancy should be mandatory. The danger of a fatal outcome for the mother is such a real possibility that delay should not be tolerated. At first this recommendation seems radical (Table I). However, when it is realized that once the renal cortex is extensively involved there is nothing the physician can do to influence the downward course of the disease, this attitude does not appear to be extreme. Furthermore, as the product of conception will very often be lost either through intrauterine death or abortion, it becomes even more evident that the evacuation of the uterus is not only a conservation procedure, but that it cannot be employed too early once the existence of extensive renal involvement has been established (Table II).

It is very gratifying to note the large proportion of patients who show a prompt remission of the more acute symptoms after the uterus has been emptied. This is to be explained by the release of pressure upon the ureters, cessation of back pressure upon the kidney pelves, and the improved drainage of the tract which follows.

The treatment of postpartum pyelitis either in the acute or subacute phase takes a very different form from that which has been outlined as applicable to the woman while the child is still in utero. In the puerperium we can safely apply the newer and more efficient methods of chemotherapy without danger. These take two general forms. The first and older method utilizes the principle that beta-oxybutyric acid in a markedly acid urine will quickly sterilize the urine of colon organ-

isms. The second employs mandelic acid salts which, when taken by mouth, are excreted in the urine and similarly are found toxic to colon organisms when the urine has a marked acidity. To produce the necessary urinary acidity necessitates some degree of acidosis on the part of the woman, the CO_2 combining power of the blood being depressed as low as 35 volumes per cent in some of our patients. Hence, these methods are probably not safe during pregnancy and should be confined to the puerperium until more is known concerning the actual danger their use may involve. It has also been considered unwise to allow nursing to continue during the course of this treatment.

TABLE I. MATERNAL MORTALITY—PYELOURETERITIS AND IMMEDIATE SEQUELAE

Sept. 1, 1932, to Sept. 30, 1936—New York Lying-In

I.	Patients with pyeloureteritis	136
	Patients with pyeloureteritis and excessive nonprotein nitrogen retention (above 50 mg. per cent)	16
		120
	Therefore 120 may be assumed to have had simple pyeloureteritis and 16 pyelonephritis.	
II.	Deaths in the group of 120 cases of pyeloureteritis	0
	Deaths in the group of 16 cases of pyelonephritis	4
	Therefore the death rate is 25 per cent in pyelonephritis or 2.9 per cent in the whole group of upper urinary tract infections.	

TABLE II. INFANTILE MORTALITY IN PYELOURETERITIS OF PREGNANCY

Sept. 1, 1932, to Sept. 30, 1936—New York Lying-In

Full term + premature infants alive	121	
Stillborn + deadborn	11	
Neonatal deaths	7	
Total births	139	
Incidence of infantile mortality associated with pyeloureteritis		12.949%
Incidence of infantile mortality from all causes		4.22 %
Infantile mortality is therefore increased three times normal experience		

The beta-oxybutyric acid bodies are induced in the urine by a ketogenic diet. This is an adequate diet in the sense that it provides a sufficient number of calories, but it contains such a high content of fat as compared to the carbohydrate component that incomplete oxidation occurs, ketosis results and the ketone bodies, chiefly beta-oxybutyric acid, are excreted in the urine. The treatment is efficacious if the urine can be kept sufficiently acid. This sometimes requires the administration of ammonium chloride if the urine is to reach the optimum acidity which is about pH_6. However, it is often difficult to gain the cooperation of the patient in carrying out this therapy, because the diet is a discouraging one to maintain. Another form of ketogenic diet based upon

the starvation principle has been more successful. With this a fairly well-balanced diet is possible, but an insufficient number of calories are given to maintain the body. In addition the carbohydrates are reduced. The effect of the diet is the same in producing the ketone bodies, but is associated with considerable weight loss. Of the two, the latter has been much the more successful in our hands, and has been most useful in combating deep-seated infection. However, both these ketogenic diets are being displaced in the treatment of pyelitis by the newer mandelic acid therapy.

Mandelic acid and ammonium chloride are combined to form an elixir which may be taken by mouth so that the patient receives in divided doses approximately 12 grams of the mandelic acid salt per day. Fluids must be limited to 1,500 c.c. or 50 ounces per day to prevent too great dilution of the mandelic acid salts in the urine. The therapy is not efficacious unless the urine can be maintained with a pH of 5.5. To control the latter, it is necessary to test the urine daily with an indicator such as methyl red, which changes color at a pH of 5.5. Occasionally an additional amount of ammonium chloride must be given to attain the desired degree of acidity, because patients vary markedly in response to the treatment. The mandelic acid treatment is given for a period of ten days; the urine is then cultured to determine whether or not the infection survives. If it does persist, the patient must be given a week's rest and then a new regime commenced repeating the same general precautions. A series of three negative urine cultures at weekly intervals are accepted as proof of a cure.

We are using the mandelic acid therapy in our postpartum patients and feel that it promises to give better results than the ketogenic diets because the patients are more cooperative in its use. We have not, however, applied it to the treatment of the antepartum patient because of the acidosis it produces. Its use is also confined almost entirely to patients with colon bacillus infections. Streptococci and staphylococci are little influenced by it. Proteus infections are resistant to this and any similar therapy which depends upon an acid urine, because this organism splits urea into ammonia which in turn alkalizes the urine and prevents the necessary degree of acidity being reached. Hence the necessity for knowing what organism is to be treated is quite obvious.

It would be a mistake not to point out the importance of antenatal prophylactic care in the prevention of pyeloureteritis and its sequelae. By encouraging all gravid women to drink copious amounts of fluids, at least three quarts a day, to rest in recumbent position for several short periods, as well as to carefully regulate the daily evacuation of the large bowel, much can be accomplished in reducing the incidence of the disease. In addition, the patient should be frequently questioned as to urinary symptoms, particularly hematuria and backache. When

these appear, especially if accompanied by a fever or chill, the course of the disease can be minimized markedly by prompt institution of the palliative therapy which has been outlined.

In closing, it may be well to emphasize a few points which are essential in the treatment of the disease:

1. It should always be remembered that upper urinary tract infections are seldom eradicated during pregnancy when once there has been a sharp febrile reaction.

2. Pyelonephritis is a very serious complication which carries with it a definite mortality. Our only method of determining whether or not it is present is the chemical examination for excessive amounts of non-protein nitrogen in the blood. When the diagnosis is made, evacuation of the uterus is indicated.

3. Bilateral pyeloureteritis presents a very serious hazard to the expectant mother. If it does not yield promptly to conservative treatment, termination of the pregnancy should be seriously considered.

4. Postpartum treatment is necessary until such time as repeatedly negative urine cultures have been obtained.

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In the world literature are records of about 200 cases of rupture of the symphysis. Between 80 to 85 per cent of these were traumatic in origin and arose during operative deliveries. The remainder were spontaneous ruptures which occurred after spontaneous labors. Since, however, when the child is forced through the birth canal, considerable force is exerted in all directions, these ruptures also entail some degree of trauma. Hence a true spontaneous rupture of the symphysis is one in which there is neither external nor internal force. Hirsch reports such a case. The rupture occurred between the eighth and ninth months of pregnancy in a woman who did not have any trauma or pathologic bony process. The author believes the cause of the rupture was a pathologic degree of physiologic softening and relaxation of the symphysis. This in turn was due to a disturbance in the responsible gland of internal secretion.

J. P. Greenhill.

END-RESULTS OF URINARY TRACT INFECTIONS ASSOCIATED WITH PREGNANCY*

E. Granville Crabtree, M.D., Boston, Mass.
In Collaboration with Dr. George C. Prather and Dr. Edwin L. Prien
(From the Urological Department of the Boston Lying-In Hospital)

END-RESULTS in urinary tract infections associated with pregnancy are, for the most part, rate of recovery from the infection, relation of such infection to subsequent pregnancies and the ultimate fate of the kidney. It was not always so. Infection of the urinary tract is capable of contributing to both maternal and fetal mortality in a large way. That it no longer does in the modern maternity clinic is due to better management which the last two decades of study of the problems concerned have made possible.

Present-day maternity clinics turn out four types of infection cases for aftercare. These are convalescing predelivery infections which have given no postpartum problems; second, infections involving the kidneys, which were not present during the pregnancy but took place during the puerperium; and third, cystitis cases without upper urinary tract involvement. These latter represent retentions and residuals following parturition where either intermittent catheterization or constant drainage has had to be employed and resulted in introduced infection. Fourth, pyelitis in pregnancy may also show pyelitis symptoms in the puerperium.

At the Boston Lying-In Hospital all such cases are directed to the Out-Patient Department clinic where they are followed until recovery takes place, a subsequent pregnancy intervenes, as all too frequently happens, or the case is restudied because of failure of the infection to clear.

Throughout all these studies of recently pregnant women one is impressed with the promptness as well as the completeness of cessation of all symptoms in prenatal infections on delivery, and the rarity of renal and cystitis symptoms in recently pregnant women. These factors added to ready disappearance of pus but persistence of bacteria lend a false security to the patient, mislead the obstetrician who relies on tests for albumin and pus without cultures or stained sediments, and falsify statistics. In these studies clearance of the urine of bacteria as demonstrated by sediments or cultures, or both, maintained over a period of one month without treatment, is the criterion for cure.

*Read (by invitation) before the New York Obstetrical Society, January 12, 1937.

In this study pH determinations are recorded. I am not sure of their significance. They might differ in untreated cases from the average range for normal adults of the same age group, since there is variation of the pH of the blood stream in pregnancy toward the alkaline side (Peters and Van Slyke). The normal range of pH for young adults is given by Peters and Van Slyke as pH 5.0 – 6.8 with a blood plasma pH of 7.4 which is a quite stationary figure. For want of a better setup the pH readings were made by means of the LaMotte indicator. For purposes of comparison pH 5.5 is selected as the division between acid and alkaline groups because it is at approximately this figure that bacteriostatic action due to acidity is supposed to begin. It is recognized that acidity alone is not bactericidal; yet our present knowledge of the constitution of the urine is not sufficient to enable us to deny the presence of normal antiseptic substances which are potent in acid urines. The basis of this statement is my observation that infections resulting from bladder or renal surgery which clear promptly and spontaneously are usually in strongly acid urines. It is also recognized that the type of infection in urine may influence it for greater acidity or alkalinity than is normal for that urine.

It is our practice at the Boston Lying-In Hospital, Out-Patient Department, to restudy infection cases which fail to clear by the end of the fourth month after delivery, with the purpose of determining the possible causes for persistence of infection. These causes may be found in the general condition of the patient; the renal condition; or the bladder condition.

The bladder is particularly conspicuous in this field because of the frequency of postpartum retentions and residuals. There is also the problem of bladder base injury which eventually results in cystocele formation. From the rarity of the finding of cystoceles in women of the child-bearing age in our clinic, and the eventual complete disappearance of bladder residual in most postpartum cases, even though bladder base injury is demonstrable, one must consider cystocele as a condition which is produced gradually after the injury occurs through loss of tissue resiliency and repeated functional stretchings of a weakened area.

Theoretically, retrogressive renal and ureteral changes begin immediately on delivery. In the majority of pregnant women they occur at a sufficiently rapid rate to give normal pyelography and a return of the pain reflex on distention through a ureteral catheter at the end of the fourth month, by which time the greatest numbers of recoveries from infection have taken place. In some instances, in spite of the absence of obstructive factors, this change is delayed much beyond this time limit. Where obstructive factors exist, not only does the retrogression

not occur above the point of obstruction, but through the lapse of time the condition progresses, because of further relaxation of the pelvic and ureteral musculature and the damaging effects of infection, an important item of which is probably mucosal edema and later chronic infiltration, which tend to increase obstruction (Fig. 1).

The presence of endocrine action as a factor in producing ureteral and pelvic dilatations in pregnancy is probable. If it occurs it probably appears early in pregnancy. Wilson and Abramson have shown that relaxation of the symphysis occurs in the first months of pregnancy. The occasional case is noted (see Fig. 2) in which, in the ab-

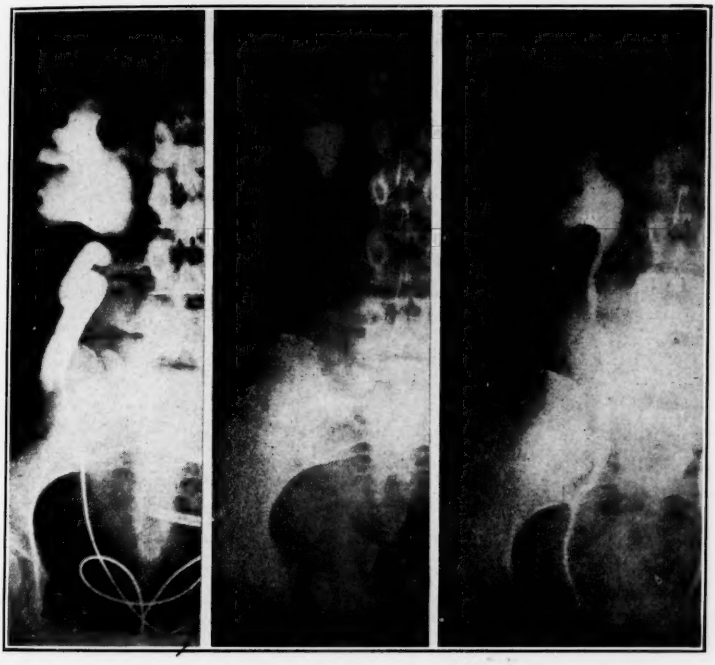

Fig. 1.—This series of pyelograms of the right kidney were made, reading from left to right, in December, 1935, April, 1936, and December, 1936. The patient was primiparous. Delivery was by cesarean section. There was neither bladder nor lower third of the ureter pathology. Birth canal injury was of course absent. Acute pyelitis in pregnancy was present but toleration for infection was acquired and the pregnancy completed. All pyelograms shown were made postdelivery. More than a year elapsed following delivery before retrogressive changes took place spontaneously and the infection recovered.

sence of either upper or lower urinary obstruction, marked degrees of dilatation of the ureters and pelvis persist which often become pyonephrotic. The obstetrical history is that of multiple pregnancies in rapid succession. Cases with a similar history but with pendant abdomens which would remove uterine pressure from the ureters have been found with minor degrees of dilatation but absence of the pain reflex on overdistention.

Cystitis cases constitute the simplest field for study of infections as such, since the only possible complicating factors are the general condition of the patient and the presence of residual urine in the bladder, which is easily determinable. They have been purposely studied irrespective of the type of bacteria concerned in the infection. The results of observations on this group are shown in Tables I to III.

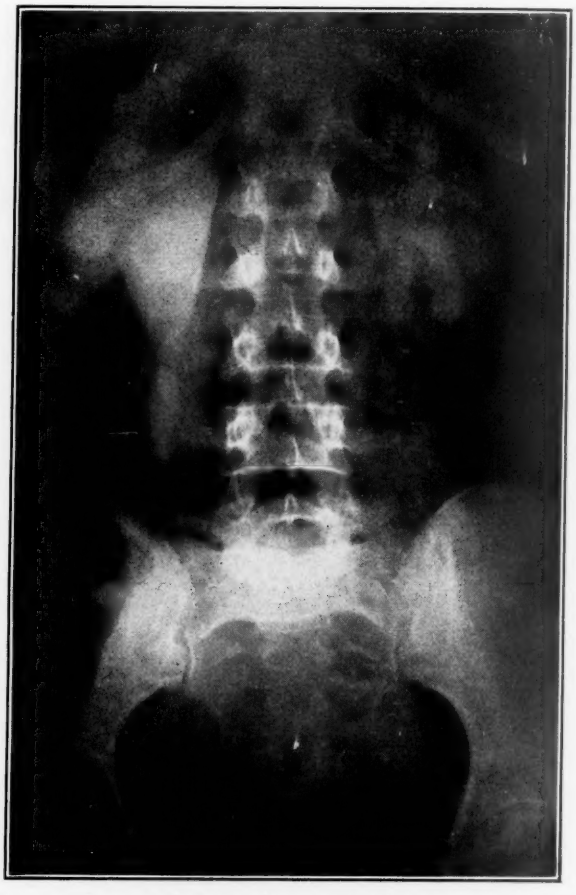

Fig. 2.—This excretory pyelogram shows extensive, and apparently permanent, bilateral, renal damage in a woman who has had eight pregnancies in ten years. The pyelography is remote from delivery (over one year). Pyelographic studies show no obstructive cause for hydronephrosis. Both kidneys have been explored surgically. No obstructive factor was demonstrated. Secondary small calculi situated in a calyx were present on the right.

TABLE I. RATE OF RECOVERY OF CYSTITIS CASES
68 CASES

WELL IN	1 MONTH	2 MONTHS	3 MONTHS	4 MONTHS	UNCURED
	38	20	3	2	5

Cases well in one month

Without treatment	37 cases pH below 5.5 = 13.0 pH above 5.5 = 9.
With treatment	1 case sent out of hospital on Hexamethylenamin.
	38

Patients who were found to have recovered in two months after delivery consisted of two groups. The first group consisted of those patients who recovered without treatment of any kind, and the second group of those in whom some treatment was given.

Patients who recovered in two months without treatment were 11 of the 20 studied.

TABLE II

Patients not seen until two months, 8. AVERAGE pH READING	Patients seen but no treatment given, 3. AVERAGE pH READING
(1) 6.5	(1) 5.0
(2) 5.0	(2) 4.5
(3) 4.5	(3) No record
(4) 5.0	
(5) 7.0	
(6) 7.0	
(7) No record	
(8) 8.0	

It is possible that some of these patients had recovered before the date of their first visit to the clinic at the end of two months and may belong in the first group of one-month cases.

The pH readings seem to bear no relation to recovery rate.

Patients who recovered in two months with treatment given were 9 in number.

TABLE III

℞ Hexamethylenamin on spontaneous acidity—2 cases.	℞ Ammonium Chloride and Hexamethylenamin—7 cases.	
(1) Average pH 5.0 (bladder residual ½ oz.)	Original pH	Acidification
(2) pH 4.5, 6.0, 5.0.	(1) 6.0	4.5
	(2) 6.0	5.0, 4.5 Residual ½ oz.
	(3) 7.0	
	(4) No record	4.5, 5.0
	(5) 6.0	5.5, 4.5
	(6) 7.5	5.0, 4.5
	(7) 8.0	5.0, 5.0
		5.0, 5.0

TABLE IV

Patients who recovered in three months were but 3 in number.

	AVERAGE pH
(1) Not seen previous to the 3rd month	7.5
(2) Not well at one month, not seen subsequently until 3 months	5.0
(3) Known not to be well during 1st and 2nd months	4.5, 5.5, 4.5

There were no bladder residuals.

Patients who recovered in four months were but 2 in number.

(1) Untreated, not seen before fourth month. No pH recorded.
(2) Treated with Hexamethylenamin on spontaneous pH 5.5, 5.0, 5.5, 5.0.
There were no bladder residuals.

Five patients were uncured when last seen.

(1) Bladder residual ½ ounces. pH reading—no record. Not seen after 1 month.
(2) Bladder residual 2 ounces. pH reading—5. Not seen after 1 month.
(3) Bladder residual 0 ounces. pH reading—5. Not seen after 1 month.
(4) Bladder residual 0 ounces. pH reading—5. Not seen after 1 month.
(5) The fifth case was returned to hospital in the first month for gross pathology.

But 2 of these 9 patients had adequate pH readings for effective administration of formalin bearing drugs. All cleared up on acidification with formalin bearing drugs added. In view of the small number of patients who appear in the third group who recovered in three months without treatment, the need for treatment is not proved in spite of alkalinity of the urine.

In consideration of renal infections associated with pregnancy, cognizance should be taken of previous lines of thought, present expediency and completeness of investigation to include at this time what data I have concerning the significance of cured infections which existed historically previous to marriage and also of known infections which were present at the beginning of childbearing. The suitable cases at my command are limited in number. I will give them for what they are worth. These cases were studied in detail so that they might be safely used here.

TABLE V

Effect of Cured Preexisting Urinary Tract Infection on Incidence of Pyelitis in First Pregnancy. Gross Pathology Excluded.

Old history of febrile urinary tract infection	1	
Pyelitis 9 years ago at Children's Hospital	1	
Pyelitis in infancy	7	9 total

None showed febrile pregnancies or infection

While there were no urinary tract infections in this small group of studied cases, there is no reason why such cases should not participate in the normal incidence of infections associated with pregnancy.

Preexisting uncured urinary tract infections without gross pathology: infections known to be present at inception of pregnancy.

2 Postmarital pyelitis and cystitis.
1 Pyelitis one year preceding marriage (cured in pregnancy).
1 Cloudy urine as a child, recurred 2 years before marriage.
1 Pyelitis 3 years preceding marriage.
5 Total.

All five patients had pyelitis in pregnancy. One was cured in pregnancy. From this small group of cases, it is to be expected that in comparatively recent persistent infections there will be a febrile course to the initial pregnancy.

TABLE VI

Tolerance for Infection

109 infected pregnancies in 52 women. The infected pregnancy was not always the first pregnancy.

	Febrile	Afebrile	
First infected pregnancy	48	3	
Second infected pregnancy	23	26	
Third infected pregnancy	2	7	
	73	36	Total 109

In compiling these statistics no note was made as to whether infection was present previous to marriage to explain the occurrence of

three afebrile first pregnancies. First infected pregnancies are quite decidedly more prone to have febrile reactions than subsequent ones. While no statistics can be given because of lack of complete pyelographic studies in all, there were instances in subsequent pregnancies where large pelvic and ureteral dilatation existed without fever's being shown at any time in the course of gestation. The figures justify the statement that the first of a series of infected pregnancies is more likely to show febrile symptomatology, but that due to acquired tolerance subsequent pregnancies, even though infection persists, are less likely to show pyelitis symptoms.

FATE OF UNCURED URINARY INFECTIONS IN SUBSEQUENT PREGNANCIES

In this study group are cystitis cases, pyelitis of pregnancy cases, and postpartum infections. A subsequent impregnation took place while infection was still present as shown by the bladder urine tests.

The first table indicates that if multiple infected pregnancies take place, irrespective of when in a series of pregnancies the first infected pregnancy occurs, infection can be expected to persist through subsequent pregnancies until cure between pregnancies can be accomplished. Naturally only women with several pregnancies could be selected for such a study (63 women).

TABLE VII

54	85.7% infected pregnancies (2-6 in number) were in sequence.
9	14.3% had one or more intervening uninfected pregnancies.
63	

Observers agree that persistence of the infection between pregnancies may be indicated by bacteriuria alone.

In consideration of the fact that there was not appreciable difference noted between the rate of recovery in pyelitis in pregnancy, postpartum pyelitis, and combined pyelitis in pregnancy with postpartum pyelitis, no separate listing is made and all are included under renal infections.

Rate of recovery in renal infections shows that 66 per cent of the cases are well in four months after delivery in untreated cases in a series of 44 cases studied:

TABLE VIII

	1 MONTH	2 MONTHS	3 MONTHS	4 MONTHS	TOTAL
Cured	8	11	6	4	29—66.0%
Last seen uncured	2	2	2	3	9—20.4%
Uncured at 4 months, returned for investigation					6—13.6%

The literature presents little end-result data. Dodds records the following data at the end of one year following delivery.

Postpartum bladder residuals which persist much beyond discharge from hospital are not common. Data as to 10 cases observed show the following. These ten cases represent the total number of residuals found in 217 cases studied at the end of one month or longer after delivery.

TABLE IX

Pyelitis in pregnancy		
Cured	49%	half in three months.
Chronic pyelitis	35%	
Bacteriuria	16%	
Postpartum pyelitis		
Cured	60%	
Chronic pyelitis	10%	
Bacteriuria	20%	

TABLE X

½ OZ. RESIDUAL	1 OZ. RESIDUAL	1-2 OZ. RESIDUAL	3¾ OZ. RESIDUAL
Well in 1 month 1		Uncured 1 mo. 1	
Well in 2 months 3	Well in 3 mo. 3	Uncured 4 mo. 1	Uncured 1 year 1
4	3	2	1

Total 10

TABLE XI

1. No assignable cause found		1	
2. Neurosis, debility, negative urinary tract		1	Debility
3. Anemia, debility		2	
4. Nephritis, debility		1	
5. Congenital strictures lower ends both ureters		1	Anomalies
6. Double ureters with hydronephrosis		1	
7. Persistent pelvic and ureteral dilatations			
Right side only	2		Effects of pregnancy
Bilateral	1	3	
8. Pyonephrosis			Effects of pregnancy with anomalies or gross pathology
Diagnosed by surgery	2		
Diagnosed cystoscopically	2	4	
9. Bladder residual 3¾ ounces		1	Bladder
Total		15	

The findings in 15 renal cases which were returned for investigation for persistent infection beyond 4 months after delivery whether treated or untreated show the following causes for failure of recovery: Debility, renal anomalies, persistence of pregnancy changes, persistence of pregnancy changes with gross pathology or anomaly background progressing to pyonephrosis and bladder residual.

Table XII indicates that any persistent infection which either is present before pregnancy or persists between pregnancies may give *febrile* reactions during pregnancy. Forty-three cases studied.

Note that three cystitis cases gave febrile upper urinary tract symptomatology in the course of the next pregnancy.

Table XIII compiled from still another group of cases shows a majority of recurrent infections take place in the uncured cases. Forty-seven recurrent infections in subsequent pregnancies.

TABLE XII

21 Infections following pyelitis during gestation.
10 Infections following postpartum pyelitis.
9 following preceding intercurrent infections.
4 pyelitis between pregnancies not due to the preceding pregnancy.
1 uncured for some years preceding pregnancy.
1 postmarital infection uncured.
3 cases with infected gross pathology (stones, etc.).
9
3 cystitis cases without upper urinary tract infection.
43

TABLE XIII

36 75.5% occurred in uncured cases
11 23.5% occurred in cases cured between pregnancies
47 Total

The fate of cured cases after one or more infected pregnancy
89 cases studied
13 14.6% had pyelitis in pregnancy.

Vinay early called attention to the tendency of pyelitis to occur in subsequent pregnancies. Thirteen women of his group became reinfected.

Maujaka found 10 of 28 cases recurring.

Dodds' series showed 14 subsequent pregnancies, 3 of which were not yet at term, with four recurrences, 2 of which were hold-over infections.

Of Klaften's five subsequent pregnancies, 2 were uninfected, 2 had febrile pyelitis, 1 was a pure bacilluria.

There is an occurrence of infections in cured cases beyond the normal incidence of 1.5 per cent which is now coming to be accepted as the expected incidence for pyelitis in pregnancy in the general run of pregnant women. Several possible reasons can be suggested for this occurrence.

1. Failure of the pelves and ureters to undergo complete retrogressive change before the subsequent pregnancy. Stasis remaining is more likely to arrest and hold a bacterial invasion.

2. Failure to recover from the debility which the first infected pregnancy produced before the subsequent pregnancy.

3. Doubt as to the certainty of cure. I question that it is possible to determine certain cure within the time intervening between pregnancies in some cases.

BACILLURIAS DURING PREGNANCIES

Bacillurias in pregnancies without pyuria or pyelonephritis symptoms often accompanied by striking degrees of pelvis and ureteral dilatation seem to indicate that once tolerance for infection is acquired the pregnancy may proceed to completion with no other evidence of infection than the presence of bacteria in the urine. The following table illustrates the location of these bacillurias in respect to parity.

One hundred nine cases of multiple infected pregnancies, parity up to xii, showed 16 pregnancies in which the infection remained a symptomless bacilluria.

TABLE XIV

PARA	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	TOTAL
	3	4	1	4	1	0	0	1	1	0	0	1	16

The distribution of these cases numerically, according to the parity, is somewhat misleading since the number of women with completed pregnancies beyond 6 is not large. Miscarriages, due to whatever cause, were eliminated when considering the pregnancy infection as a pure bacilluria.

The three para i infections which remained bacillurias were in cases which were either of long standing, such as persistent pyelitis of infancy or were associated with chronic gross pathology also of years' duration.

THE FATE OF THE CHILD IN PYELITIS OF PREGNANCY

The pediatricians of the Boston Lying-In Hospital assure me that they cannot distinguish, by physical findings, a child born of a pyelitic mother from other infants. Unless premature these children equal the average in regard to nutrition, weight, and physical development. Likewise they are no more prone to anemias, feeding problems, or incidence of intercurrent disease.

It must not be forgotten that the acute phases of pyelitis, especially with dehydration, nausea, toxicity and consequent malnutrition, produce anemia very rapidly in pregnant women. Where the condition remains subacute with frequent exacerbations for several weeks or even months severe degrees of maternal anemia may result. Red cell counts as low as 1,500,000 with hemoglobin readings of 20 per cent have been noted in one patient whose physician placed her on a diet of orange juice and crackers over a febrile period of almost four months.

Minot, Straus, Castle, Rowland, Galloway, Wells, Talpade and others have studied both the nature of the anemias in pregnancy and the effect upon the child. They recognize four types of anemia.

TABLE XV

Dilution anemia 60%–70% Hg. 3,000,000 red cell count.
Pernicious anemia (the few pernicious anemia patients who become pregnant), red cell changes typical.
A pernicious anemia of pregnancy 30% to 40%.
Slow developing secondary anemia, variable in severity.

Dilution anemia is supposedly due to increased blood volume in pregnancy but the blood smear remains unchanged. It is, therefore, only a relative anemia. It needs no treatment.

The more profound type of rapidly developing "pernicious" anemia and the slower progressive anemia which show the blood picture of secondary anemia in various degrees of severity require treatment. Many pregnant women show hypochlorhydria. Castle has shown that these

require both blood-building foods, such as beefsteak, and gastric juice in order to gain by diet alone. In these groups there is much evidence of dietary deficiencies. Treatment is by blood-building diet, iron, vitamin B, and liver extract. The action of vitamin B (yeast) and liver extract is inhibited by septic infection.

Straus indicates that in even severe untreated anemic mothers the child is born with normal hemoglobin, ranging about 100 per cent. After a few months the child falls into anemia during its first year. If the mother is adequately treated the child does not develop this anemia.

So far as infection is responsible for maternal anemia the child born of a pyelitic mother may suffer anemia during its first year, although born with a normal blood picture in spite of the degree of anemia which the mother may have.

In severe degrees of maternal urinary tract infection prematurity is the chief danger to the child. Tuberculosis of the kidney which has its inception during pregnancy is fortunately extremely rare. It accomplishes the complete destruction of the kidney or kidneys involved during the course of the pregnancy. When diagnosed immediate interruption is indicated. Pregnancy in chronic tuberculosis is not the same problem.

Diabetes together with pyelitis in pregnancy also rates interruption in our hospital. Occasional cases of virulent infections, especially where the organism is streptococcus, we also feel rate interruption. We recognize that intractable cases can be carried over to term if nephrostomy or pyelotomy is done. We hesitate to advise a procedure applicable to only a part of the childbearing life of a woman. The first renal operation is much easier to advise than subsequent ones since repeated operations on the kidney are both difficult technically, and endanger the integrity of the kidneys so treated. We prefer to interrupt intractable cases, cure infection, then re-engage in childbearing.

If the maternal anemia and infection of the urinary tract during pregnancy receive prompt recognition and modern treatment, loss of fetal life and prematurity will furnish but a negligible number of handicapped children in the wards of your hospital.

There is no indication, whatever, that the child participates in the mother's urinary tract infection similarly to congenital acquisition of syphilis.

CONCLUSIONS

1. Postdelivery urinary cases are of four types: Cystitis, pyelitis in pregnancy, pyelitis in the puerperium and those who have had pyelitis in pregnancy and also in the puerperium.

2. The majority of cystitis cases recover in the first month after delivery. The majority of renal infections clear within four months after delivery.

3. There is little difference in the rate of recovery among pyelitis in pregnancy, pyelitis in the puerperium and combined cases. They are best considered under the common heading "renal infection."

4. Renal infections which fail to clear within four months commonly do so because of four factors:

a. Debility of the patient.
b. Abnormal persistence of pregnancy renal changes.
c. Abnormal persistence of pregnancy renal changes with anomalies or gross pathology.
d. Bladder damage with residual urine.

5. A previous history of cured urinary tract infection without abnormalities of the urinary tract probably does not influence the incidence of pyelitis of pregnancy.

6. Infections which are uncured at the beginning of the first pregnancy probably produce febrile pregnancies in most cases.

7. Tolerance for infection either independent of pregnancy or associated with it seems to be acquired in many cases of long-standing infections. Such cases may be free from febrile symptoms during subsequent pregnancies or remain bacteriurias.

8. If multiple infected pregnancies occur in a series of pregnancies they are apt to be in sequence. The majority of recurrent infections in pregnancies take place in uncured cases but there is a higher incidence than normal in these "cured" cases.

9. Any form of urinary tract infection, even cystitis, may give rise to febrile pyelitis in subsequent pregnancy.

10. Infections which persist into the next pregnancy may remain symptomless bacteriurias, in spite of large renal and ureteral dilatations.

11. Residual bladder urines are not common in postdelivery cases, even though the injury from which cystocele eventually develops must be present. Cystocele, therefore, probably develops slowly following birth injury.

12. Small bladder residuals, under one ounce, seem not to retard spontaneous recovery from infection. Residuals above two ounces probably are of significance.

13. Children born of pyelitic mothers are not abnormal unless prematurity results from the severity of the infection.

14. Maternal anemia due to urinary tract infection or other causes may harm the child during its first year, although it is usually born with a normal hemoglobin.

15. Urinary tract infection as such is not transferred from mother to child as is congenital syphilis.

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DISCUSSION ON PAPERS OF DRS. TRAUT AND CRABTREE

DR. HENRY G. BUGBEE.—The clinical picture in these cases, as I saw them in 1911 as urologist to the New York Lying-In Hospital, was characteristic. There was often an early history of a chill, followed by fever, perhaps with nausea and vomiting, always with abdominal distention, pain, and tenderness in the costovertebral angle. During this stage, urinary symptoms were rarely present, and the urine was often free of pus or contained only isolated cells, while bacteria were commonly found on smear or culture. As the bacteria were almost invariably colon bacilli, the first indication seemed to be a thorough clearing out of the intestinal tract, followed by colon irrigations with forcing of fluids to increase kidney elimination.

With the establishment of kidney drainage, costovertebral tenderness invariably subsided and bladder symptoms (dysuria) supervened, the urine then showing quantities of pus and large numbers of bacteria. If kidney drainage did not take place at once, ureteral catheters were passed and retained if necessary. When the catheters were passed unmistakable signs of retention of urine beyond a point of ureteral occlusion were almost invariably present, the occlusion being most often in the lower ureter on the right side.

Urinary antiseptics were then found to be efficacious, and with the subsidence of the acute infection, every effort was made through forced elimination, intestinal and urinary, to carry the patient through the pregnancy. The knee-chest position for certain periods of the day was found beneficial, and after delivery a study of the urinary tract was carried out to ascertain the possible existence of an underlying urologic lesion.

As time passed, I was called upon less frequently to see these cases, as the prophylactic care which was instituted by the members of the staff was efficacious in preventing many infections. In other instances, the infections were so much less severe that they responded readily to routine medical treatment.

A great variety of underlying lesions of the urinary tract was found, over a period of twenty-three years, consisting of the following anomalies: pressure upon the kidneys or ureters, causing displacements and narrowing of the lumen of the ureters; constrictions secondary to anomalous vessels; strictures of the ureters; the presence of a tumor of the urinary tract; calculi; even polycystic and ectopic kidneys. All of these gave impaired urinary drainage and thus predisposed to infection. Focal infections in various parts of the body were often discovered and eliminated. Yet in a large proportion of cases, pressure upon the ureter by the uterus, with atony of the ureter and the kidney pelvis, was the only anatomic lesion present. The same observations have been made in the service at the Woman's Hospital over a corresponding period. During the past year there were

869 cases in the Obstetrical (ward) Service at the Woman's Hospital. In these 869 cases, there were 30 kidney infections, only 9 of which required ureteral catheterization.

As time has passed, I have had no reason to change my views upon this subject, and still feel that the same principles underlie the causation and treatment of kidney infections in the pregnant woman as in the nonpregnant, due allowance being made for the child.

DR. NATHANIEL P. RATHBUN.—Dr. Traut has made a distinction between pyeloureteritis and pyelonephritis. I am rather disposed to think that most of these cases are pyelonephritis and probably also ureteritis. I am not so sure that the blood chemistry index can be made the basis for differential diagnosis. It may be a criterion of the degree to which the kidney is infected, but I am of the opinion that all cases of pyeloureteritis are actually pyelonephritis as well.

In the matter of drainage there are several points about posture which are important. In the early months of pregnancy, when the uterus is riding on the pelvic brim, a little Trendelenburg posture is desirable, whereas in the later months of pregnancy the reverse of that, the Fowler position, is preferable. In many of these cases, particularly in the puerperium, but sometimes actually during pregnancy, there is a disturbance in the evacuation of the bladder. Some of these patients do rather well with an indwelling bladder catheter to keep the bladder empty. Dr. Crabtree remarked that he noted residual urine in comparatively few of these cases, but my experience has been that a good many of them have residual bladder urine.

During the febrile period, while I appreciate the fact that the colon bacillus is best attacked by various antiseptics effective in an acid medium, I am disposed to give these patients at first some form of alkaline diuretic. The urinary antiseptic for an acid medium can only be effective with a concentrated urine, and in these early cases we want to have a dilute urine, an alkalosis, and some form of diuretic to promote the flow of urine.

Another point of importance about the treatment of pyelitis during the puerperium is the necessity of complete and careful irrigation of the bladder and of the kidney pelvis. Sometimes it is desirable even in the acute cases to leave a catheter in the ureter, although I find occasionally that an indwelling ureteral catheter plugs the ureter rather than drains it.

DR. HENRY D. FURNISS.—I do not know whether we are justified in speaking of "the pyelitis of pregnancy," or whether we should term it "pyelitis and pregnancy." There have been a number of my patients with ureteral strictures who have subsequently become pregnant. I have predicted trouble for them and have seen my prophecies come true.

In pregnancy there is a normal dilatation of the ureter from hormonal action. With this normal dilatation plus a pathologic obstruction we have a combination which predisposes to infection. Kidd, in his book *Infections of the Kidney*, brought out the very illuminating observation that we are constantly absorbing into the blood stream bacteria from the intestinal tract. When well, and our resistance is good, the bacteria are normally killed off, but if anything occurs to lower this resistance we are very likely to be a prey to these bacteria. This may be brought about through overwork, mental strain, chilling, and intestinal derangement. In uncomplicated cystitis the factor of exposure to cold has been the greatest precipitating cause I have found.

The fetus is affected adversely in many of these cases, and while not apparent at the time of birth, these children are later found to be sub-standard, sometimes for a year or more.

In mandelic acid therapy we have something of value in urinary tract infections. Frequent urinalyses are necessary during the administration of the drug as many develop albuminuria and casts. I have not, however, observed the development of acidosis when this drug is used, even in pregnancy.

DR. TRAUT (closing).—I would like to clarify my use of the term pyelonephritis and am very grateful to Dr. Rathbun for pointing out what is apparently a misunderstanding.

Pyeloureteritis and pyelonephritis are clinical-pathologic terms representing the extent of involvement of a disease process. They can be used quite accurately by the pathologist, as he can examine the organs and observe the products of inflammation. For the clinician to use them correctly is a much more difficult matter and yet, as has been pointed out, it is very important for him to do so, as the first is a relatively benign process associated with no mortality, whereas the latter is an extremely dangerous complication.

The only means available for a clinical diagnosis between pyeloureteritis and pyelonephritis is the use of the nonprotein nitrogen or urea nitrogen estimation of the blood. I hoped that I had made it clear that even this test gives us the correct diagnosis only when a considerable amount of kidney damage has taken place and that its warnings are therefore very important ones indicating prompt action if the patient is to be saved. I must re-emphasize this point, for it represents the most important advance that has been made recently in the treatment of the acute phase while the fetus is still in utero.

Whether there is or is not some degree of parenchymal involvement of the kidney in every case of pyeloureteritis in pregnancy is, for the moment, of academic importance only because the opinions of authorities differ markedly. We can say, however, with certainty that in pyeloureteritis with no retention of nonprotein nitrogen in the blood stream we are dealing with a process which has not caused damage to the excretory organs of such a nature as to cause death, whereas, when nonprotein nitrogen retention occurs, grave alterations have taken place, which we choose to characterize, rightly or wrongly, as pyelonephritis and which we have learned are associated with a high mortality (25 per cent).

With the increased use of this test in pyeloureteritis of pregnancy much will be learned concerning kidney involvement on the one hand, and on the other, lives will certainly be saved if its warnings are heeded and the burdens of pregnancy promptly removed and adequate drainage established.

DR. CRABTREE (closing).—I want to make myself clear on one point. I do not deny the existence of postpartum bladder retention and residual urine while the patient is in the hospital. I am calling attention to the fact that in this series of 217 cases seen at least a month after delivery there were but 10 instances in which there was residual urine shown on repeated examination.

Barsony, Eugenio: Endometriosis of the Uterine Adnexa, Monitore ostetrico-ginecologico 8: 375, 1936.

The author after discussing the symptomatology of tubal endometriosis describes four cases of adnexal endometriosis. He analyzes the mechanism of the rupture of the adnexal sacs. On account of the resulting peritoneal irritation and internal hemorrhage, adnexal endometriosis is clinically often mistaken for extrauterine pregnancy.

AUGUST F. DARO.

A STUDY OF THE END-RESULTS OF THE TREATMENT OF AMENORRHEA AND STERILITY BY RADIATION OF 128 MARRIED WOMEN OVER A PERIOD OF TWELVE YEARS*

IRA I. KAPLAN, B.Sc., M.D., NEW YORK, N. Y.
(Director of the Division of Cancer, Municipal Department of Hospitals)

EIGHT years ago, and again in 1931, we[1] reported on our treatment of a limited number of cases of amenorrhea and sterility with x-ray therapy. Now, after observing a larger number of patients and their children over an extended period of time, in some instances ten years, we are still of the opinion that in no other field of gynecology is irradiation more helpful and promising than in the treatment of functional disturbances of the ovary and in sterility.

Unfortunately, there still exists among the profession a definite prejudice against irradiation for therapeutic purposes, based upon misconceptions or hearsay evidence of harmful effects upon both mother and offspring which are uncontrollable. Such misconceptions were recently stressed by a committee of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons,[2] who have added instances of ill effects on the offspring, totally disregarding the successful results obtained by careful workers. There is no question that irradiation during pregnancy is in many instances harmful to the unborn child, the harm depending to a great extent on the age of the embryo and the amount of irradiation given. Nevertheless perfectly healthy children have been born to mothers who were irradiated for malignant conditions during the course of pregnancy.

We reported such a case in 1930,[3] and Neill[4] recently reported a fortunate outcome in some of his cases, citing several instances reported by others. In 1926 Rubin[5] reported successful results in the treatment of patients with amenorrhea and sterility. Though his series was small it demonstrated that x-ray therapy had an appreciable therapeutic effect when applied to the pelvis and pituitary.

Further study of successful results in a larger group of cases with subsequent follow-up of children born of irradiated mothers, leads us to reiterate our previous conclusions that irradiation when properly given is neither harmful to the mother nor to the offspring and has proved a valuable therapeutic procedure for the treatment of amenor-

*Presented, by invitation, before the New York Obstetrical Society, December 8, 1936.

rhea and the relief of sterility. In a recent report by Mazer and Spitz[6] who obtained 50 per cent pregnancies in their cases, they have arrived at the same conclusion.

In our series we have had but one untoward effect, reported in 1932.[7] In this case treatment was administered when there already existed an embryo in utero, which is quite another matter than the subject under present discussion. The effect of x-rays upon the embryo is profoundly different from the effect upon unimpregnated ova.

The reason for again calling attention to this mode of therapy is warranted because no other treatment so far devised, including organotherapy, has yielded satisfactory or equally good results. The enthusiasm aroused by endocrine studies in this direction has so far led to disappointment. Stein and Leventhal[8] have shown that endocrine therapy is of no avail in cases of cystic ovaries, amenorrhea and sterility. Many of our patients received irradiation only after prolonged endocrine therapy had proved unavailing. One case in particular, a young woman of twenty-seven years had submitted to two years of persistent endocrinologic investigation and hypodermic injections. Her arms and legs had been treated like pincushions. She accepted x-ray therapy as a last resort which the result has fully justified. Having menstruated at monthly intervals for four months following the x-ray treatment, this patient is at present in the eighth month of pregnancy.

Our present report is based upon a study of 128 married women who were referred to us in private practice during the period of 1924 to 1936 for treatment of amenorrhea and sterility. An appreciable number of cases of single women treated by us for amenorrhea are not considered in this study. We have follow-up records in 114 patients. Whether or not some of the 14 who could not be traced may have responded to the treatment, they are regarded by us in this study as failures. The menses were regulated in 76 women and in 52 there was no improvement.

The oldest patient treated was forty-five years of age, the youngest nineteen. The ages in the successful group varied between twenty-one and twenty-nine years in 46 patients, and between thirty and forty-five years in 30 patients. In the unsuccessful group 25 patients were between twenty-four and twenty-nine years of age, and 27 between thirty and forty-five. We noted that the younger the patient the more amenable to treatment.

In all instances some form of endocrine therapy, including tablets of ovarian substances and the newer hormonal substances, had been used and proved unavailing. All the cases had previously been examined for gynecological abnormalities. In many histories previous tubal insufflation was recorded, and in a number of instances the husband had been examined for potency. In 8 cases previous curettage or

other surgical corrective measures were carried out. Of the 128 patients treated 43 were treated for amenorrhea varying from months to years, 41 for amenorrhea and sterility, 11 for sterility alone, and 33 for oligomenorrhea, the menstrual intervals being several months.

TREATMENT

X-ray Therapy.—In all instances treatment consisted of x-ray irradiation to the ovaries. In 80 cases an additional treatment was given to the pituitary and in 5 instances also to the thyroid. The factors used were: 200 K.V., 4 M.A., with the filter of 0.5 mm. copper and 1 mm. aluminum, at a target distance of 30 to 40 cm. Treatment was directed through 4 pelvic fields, 9 by 12, 10 by 15 cm., and to the pituitary area of 6 by 8 cm. The dose given was 75-150 r. units (measured in air) per field at intervals, one treatment per week for three weeks. Occasionally a fourth treatment was administered.

Results.—Of the 76 patients whose menstruation was reestablished, 44 patients became pregnant. In 84 instances no pregnancy occurred. Of the 44 patients who conceived, 2 are at present in the course of their pregnancy, 17 have conceived more than once, 5 conceived but aborted, 2 of these aborted twice. Thirty-six patients became pregnant and went to term, giving birth to 47 living children and one stillbirth with an abnormal fetus. Nine women have had more than one child. There was one case of twins. Of the 44 pregnant patients, amenorrhea existed from one month to fourteen years, and sterility from one to eighteen years. Only 4 patients had previously borne children, 3 had previously aborted or miscarried.

None of the patients treated were harmed in any way. In no case did menstruation cease or become scanty where menstruation had previously occurred in the usual manner.

The 36 women who bore children had amenorrhea and sterility as seen in Table I. All these patients received x-ray therapy to the pelvis and 18 received additional treatment to the pituitary. In 2 cases the thyroid was also treated.

A study of the surviving children shows them all to be normal, both physically and mentally. Reports from the parents have in no instance disclosed any abnormality, nor any physical deformities. There are 25 boys and 22 girls in this group, the oldest under study is now ten and one-half years of age. Photographs of many of these children are attached.

Abstract case histories of the 44 pregnant patients are reported.*

Now, as to the explanation of the action of the x-rays. Although in 1905 Halberstaedter[9] first demonstrated the selective action of x-rays on the ovaries, still the reaction to x-rays are not as yet clearly under-

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stood and their biologic action on the ovary not entirely elucidated. We are not yet definitely clear as to the real cause of menstrual bleeding, although recent endocrinologic studies have shown an undoubted relationship between the ovary and the pituitary. This interrelationship has been recognized for many years but recently Hartman[10] and

TABLE I

NAME	AGE	YEARS OF STERILITY	PREVIOUS CHILDREN	PREVIOUSLY MISCARRIED	AMENORRHEA	PREVIOUS OPERATIONS
R.	28	6	0	0	Irreg. 1-3 mo.	0
A.	28	4½	0	0	6	0
A.	28	2	0	0	1	0
B.	27	3	0	0	6-8 mo. scanty	1 curettage
B.	24	4	0	Feb. 1926	7 mo.	1 curettage
B.	22	1	0	Aug. 1924	3 mo.	0
B.	24	4	0	0	3 mo.	0
C.	30	8	1 still-birth	0	Irreg. 1 mo.	0
C.	26	6	0	0	Irreg. 1 mo.	0
C.	26	5	0	0	13 mo.	0
D.	32	3 (14 yr. married)	3 (youngest 6 yr.)	0	Irreg. 3-6 mo.	0
E.	24	3	0	0	12 mo.	0
E.	29	7	1 (6 yr. old)	0	5 mo.	Cervix cauterized
F.	29	3	0	0	Irreg. 2 mo.	0
F.	28	3	0	0	13 mo.	0
G.	21	1	0	0	Irreg. 3 mo.	0
G.	27	3	0	0	Irreg. 3 mo.	0
G.	34	4	0	0	Irreg. scanty	Oper. infantile uterus cystic ovary
G.	30	3	0	1924	8 mo.	Curettage
J.	30	5	0	0	14 yr.	0
K.	31	2	0	0	Irreg. 3 mo.	0
L.	22	2	0	0	Irreg. 5-8 mo.	0
L.	25	3	0	0	Irreg. 5-6 mo.	Curettage
M.	21	3	0	0	11 mo.	0
M.	23	3	0	0	5 mo.	0
M.	25	4	0	0	Irreg. 2 mo.	0
M.*	21	Not married	0	0	Irreg. 3 mo.	0
M.	34	3	0	0	Regular	0
O.	30	6	1 still-birth	0	Irreg. 2 mo.	Electric
R.	22	3	0	0	Irreg. 1 mo.	0
S.	24	5	0	0	3 mo.	0
S.	24	2	0	0	3 mo.	0
S.	33	17	0	0	Irreg. 1-4 mo.	Curettage
S.	31	8	0	0	12 mo.	0
U.	28	8	0	0	Irreg. 3 mo.	0
A.	28	4½	0	0	Irreg. 6 mo.	Curettage

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C.	26	5	0	0	13 mo.	0
D.	32	3 (14 yr. married)	3 (youngest 6 yr.)	0	Irreg. 3-6 mo.	0
E.	24	3	0	0	12 mo.	0
E.	29	7	1 (6 yr. old)	0	5 mo.	Cervix cauterized
F.	29	3	0	0	Irreg. 2 mo.	0
F.	28	3	0	0	13 mo.	0
G.	21	1	0	0	Irreg. 3 mo.	0
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G.	34	4	0	0	Irreg. scanty	Oper. infantile uterus cystic ovary
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J.	30	5	0	0	14 yr.	0
K.	31	2	0	0	Irreg. 3 mo.	0
L.	22	2	0	0	Irreg. 5-8 mo.	0
L.	25	3	0	0	Irreg. 5-6 mo.	Curettage
M.	21	3	0	0	11 mo.	0
M.	23	3	0	0	5 mo.	0
M.	25	4	0	0	Irreg. 2 mo.	0
M.*	21	Not married	0	0	Irreg. 3 mo.	0
M.	34	3	0	0	Regular	0
O.	30	6	1 still-birth	0	Irreg. 2 mo.	Electric
R.	22	3	0	0	Irreg. 1 mo.	0
S.	24	5	0	0	3 mo.	0
S.	24	2	0	0	3 mo.	0
S.	33	17	0	0	Irreg. 1-4 mo.	Curettage
S.	31	8	0	0	12 mo.	0
U.	28	8	0	0	Irreg. 3 mo.	0
A.	28	4½	0	0	Irreg. 6 mo.	Curettage

*When first treated.

his coworkers have definitely demonstrated that the pituitary is indispensable for menstrual bleeding to occur. Lacassagne[11] states that only one-third of the anterior lobe of the pituitary is sufficient to preserve genital activity and that a definite minimum of anterior lobe is required to maintain normal physiologic balance of ovarian function.

At the present time we are inclined to attach prime importance to the pituitary as the factor controlling menstrual function. Do the x-rays to the ovaries activate that "bleeding factor" of the anterior pituitary which then produces menstrual bleeding, as suggested by Wilson and Kurzrok?[12] It is evident that normal genital function of the female depends upon the proper correlation between the pituitary, the ovary, and the uterus.

Aschheim and Zondek[13] proved that the pituitary produces its effect only when the ovary is present. Allen[14] states that the anterior pituitary controls and maintains the action of the ovaries, and Novak[15] ascribes this control to the gonadotropic hormones produced by the basophile cells.

Beclere[16] was the first to report the effect of x-ray on the pituitary. Lacassagne[11] has shown that the anterior lobe of the pituitary is most resistant to destructive effects of irradiation and therefore therapeutic irradiation of the pituitary is not harmful. Werner[17] found that x-ray treatment of the pituitary stimulated menstrual reaction, and because of this so-called stimulating action Borak[18] suggested pituitary irradiation for mitigating climacteric symptoms of early menopause.

Frank[19] states that in the normal mature fertile woman the ovary secretes two hormones, the estrogenic factor and the progestational factor, and that normal genital function is dependent on the synchronism of prepituitary estrogenic and progestational blood cycles. Mazer agrees with Frank that the normal menstrual cycle depends upon the balanced activity of the two ovarian hormones. Mazer and Andrussier[20] emphasize the definite dependence of ovarian function upon hormonal stimulation from the pituitary. Corner[21] states that progestin, the hormone of the corpus luteum, will help cases of sterility and habitual abortion, due to lack of corpus luteum, as it acts as a menstruation suppressor. Allen says experiments have shown that surgical removal of the corpus lutea brings on menstruation. Cystic conditions of the ovaries may readily produce amenorrhea or sterility and, as Stein and Leventhal have shown, endocrine therapy is of little avail in such conditions, mechanical means constituting the only procedure for relieving the condition.

Although x-ray treatment of the pituitary appears to be efficacious it does not account for the favorable results in all our patients, as only 18 received this treatment.

Does x-ray act mechanically, as in the case of polycystic ovaries which are relieved (Stein and Leventhal) by mechanical destruction of the cysts? In our series, one patient had cystic ovaries, proved at operation. Sterility was relieved by x-ray therapy. Perhaps by destruction of the cysts? Does it destroy the corpus luteum which suppresses menstruation according to Corner, or does it stimulate general endocrinologic action and reaction in the body, setting in motion the

normal interchange of hormones which produce normal pituitary, ovarian and uterine function and thus allow for menstruation and subsequent pregnancy?

Hutton[22] and his coworkers in their study of the action of x-rays on the mechanism of blood pressure control have definitely shown that x-rays have an appreciable effect on the endocrine system. In our own observations[23] we have noted that irradiation of the ovaries in castration doses inhibited epileptic attacks which accompanied normal menstruation suggesting some relationship to the brain. The effect upon the rest of the endocrine system if applied to the ovaries may also be assumed to be reciprocal.

Wilson and Kurzrok[12] state that actual bleeding occurs only if the bleeding hormone is not inhibited by the corpus luteum hormone. Does the x-ray destroy this inhibitory function of the corpus luteum? In our series in which 44 patients became pregnant following x-ray treatment, 7 cases had previous pregnancies, 4 of whom bore normal children, and 3 miscarried. Perhaps these had a persistent corpus luteum which inhibited menstruation and caused subsequent sterility. X-ray therapy by destroying the corpus luteum permitted these patients to menstruate, conceive and deliver normal children. Mazer and Andrussier state that organotherapy is far less effective than irradiation of the affected endocrine glands in the successful reestablishment of menstrual periodicity. Taylor[24] likewise has shown that organotherapy is of little value in controlling mastitis associated with menstrual disorders and states that x-ray therapy is often of definite therapeutic value in this condition, the x-rays achieving the result through the endocrine system.

Wolf,[25] investigating endometrial biopsies obtained from cases of amenorrhea, states that the symptoms may be the result of:

1. Absence of function of the anterior pituitary lobe where the gonadotrophic hormones originate. The endometrium is atrophic

2. Excessive amount of follicle-stimulating hormone, producing single or multiple granulosa cysts in the ovary without corpus luteum formation. The endometrium is hyperplastic (polyhormonal amenorrhea of Zondek).

3. Excess of luteinizing gonadotrophic hormone which results in a persistent cystic corpus luteum of the ovary. The endometrium is in the premenstrual phase.

In Wolf's opinion x-ray therapy directed to the pelvis is of no avail in Group 1, yet we have very numerous instances of apparent stimulation of pituitary function in this group. In Group 2 the x-ray, he states, destroys the persistent follicle, resulting in anovulatory bleeding and the results are generally good. In the third group, x-ray, by destroying the persistent corpus luteum, causes bleeding from a premenstral endometrium. In our work with the treatment of neoplasms, we have had frequent examples of actual tissue destruction by x-rays and can readily conceive of such a result on the follicle cysts.

Whether the x-ray affects directly the ovary, the uterus, or the pituitary, or is an indefinite endocrinologic factor stimulant, may be debated. Despite this the fact remains that it has been a definite factor in the successful treatment of the cases herein reported.

The treatment must, as Mazer has emphasized, be given with care and in suitable cases.

SUMMARY AND CONCLUSIONS

X-ray therapy is of definite value in the treatment of functional disturbances of the ovary and in sterility. Irradiation is applied to the pelvis in most instances, and in some cases to the pituitary as well. Whether to treat only one or both is a matter of judgment, based on training and experience.

Careful observation over a number of years of children born of mothers so irradiated shows that such children are in nowise abnormal physically or mentally.

Detailed case reports are included in the author's reprints. They are omitted here for lack of space.

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DISCUSSION

DR. WILLIAM P. HEALY.—A communication of this kind requires serious consideration from us, because it represents observations over a period of years of a large series of cases. The literature is moreover being added to daily, indicating that there is value in this method for the treatment of amenorrhea and sterility.

Dr. Kaplan's small series of 11 cases treated for sterility only are, I assume, those patients who had a normal menstrual function. I wonder upon just what theory he expects to get a result from the treatment of these, and in what percentage a favorable result was actually obtained. I would be interested in knowing also how soon the average patient responds to the treatment for amenorrhea, and how much time Dr. Kaplan would allow before saying that the treatment was ineffectual.

The question of sterility is a different matter. Were it not for the fact that in many of these cases the patients had been treated for a long time for their sterility without avail previous to the use of the roentgen therapy, one would be inclined to say that the relationship of the conception to the therapy was unproved. Sterility is so easily and so effectually overcome by many different procedures. I think, however, we must agree that these cases represent successes achieved in instances of failure by other methods of treatment.

DR. HOWARD C. TAYLOR, JR.—The evidence which Dr. Kaplan brings, that x-ray stimulates or regulates the ovarian function, requires a consideration of the mechanism by which this is brought about. First, the x-ray may act directly to stimulate the granulosa cells, an effect difficult to prove. Second, the x-rays may be effective indirectly, through the blood vessels in the production of an hyperemia, that itself improves the nutrition of the ovary. Third, it is possible that the x-ray has a still more remote action, in that as the result of the radiation of the body in general certain protein substances are formed that actually stimulate the ovary. Finally, it is possible that the effect is produced, not by stimulation, but by the inhibition or actual destruction of certain structures in the ovary, such as follicular cysts or a persistent corpus luteum. It is the last theory which appeals to me the most.

It would be of great help if Dr. Kaplan could tell us what type of amenorrhea he has been treating. Now it is fairly well recognized that amenorrhea may be of at least two types. In one there is an atrophic ovary and an absence of estrin in the blood and in the urine. In the other type there are probably follicular cysts or persistent corpora lutea in the ovary and here there is still an ovarian function in an endocrine sense which demonstrates itself in the moderate hyperemia of the vaginal mucosa.

It is first of some scientific importance for us to know which type of amenorrhea Dr. Kaplan has been radiating. If these cases are of the atrophic type, then the effect must be some variety of stimulation, whereas if they fall in the group that are connected with follicular cysts or the persistent corpus luteum, the x-ray may have a destructive effect on some of these structures and still regulate the ovarian function.

This differentiation is also of practical importance. We should in fact know before radiating a case of amenorrhea which type we are dealing with. If we have the type of amenorrhea due to a depression of the ovarian function, the x-ray may make it worse. If we have an amenorrhea due to follicular cysts or a persistent corpus luteum, the x-ray may be beneficial.

A number of other writers have published their results following radiation of the ovary for amenorrhea and sterility. These have been collected and reported by Wintz (Wintz, H., and Wittenbeck, F. "Klinik der Gynäkologischen Röntgentherapie." Handbuch der Gynäkologie: 6: Part 1, Munich, 1933, J. F. Bergmann, p. 318.) as a series of 319 cases from about twenty different authors. In about 50 per cent of the cases of these authors, improvement in menstruation resulted, and in about 15 per cent pregnancy ensued. As I figure Dr. Kaplan's results, he has obtained about 60 per cent improvement in menstruation and about 33 per cent of the patients became pregnant.

Any results on the treatment of sterility and on abnormalities of menstruation are notoriously difficult to evaluate. I would like to know in detail how long these patients were amenorrheic, how long they were sterile, how soon after treatment they developed menstruation, and how soon after treatment they had children. I think it is very probable that some of Dr. Kaplan's patients would have become pregnant and some of them would have had a normal return of menstruation even without treatment. On the other hand, Dr. Kaplan's results are so good that we cannot deny the probability that the x-ray was an important factor in producing the reported results in many of the cases.

DR. ISIDOR C. RUBIN.—There are two or three points that I want to touch upon. First, there is the danger of an embryo being irradiated without the physician who sends the patient to the x-ray therapist being aware that the patient is pregnant. The treatment should therefore under no circumstances be instituted except within a week after a period no matter what the menstrual habit for that particular

patient may be. If you irradiate a woman who has had her period six, seven, or eight weeks ago, although she menstruates habitually every four or five months, you may strike an early period of gestation. The Aschheim-Zondek test in such instance can exclude the possibility of pregnancy.

The results promised from endocrine therapy made me, among others, abandon the radiation treatment for the time being, although I had had very good results up to 1929. Since that time I have used x-ray treatment in a few cases because hormonal therapy has proved ineffectual in this particular group. Experience has proved that the amenorrhea associated with sterility once being corrected is then followed by pregnancy in an appreciable number of cases.

The difference between x-ray therapy and the more effective hormonal substances such as progestin and proluton is also of interest. There is no doubt that the menses may be induced by such hormonal therapy once, and even twice, and in an occasional case regular periods may follow. The x-rays induce menstruation which becomes regular in the vast majority of the amenorrhea cases so treated. There is no doubt that if we could obtain effective hormonal substances to correct deficiencies in function which we could definitely diagnose that then we should have reached the ideal in therapy, for the fear is still entertained by many that x-rays have a deleterious effect upon the germ plasm. In the children so far observed born of mothers who received x-ray treatment in fractional doses I have personally not observed any signs of degeneration which confirm the observations of Dr. Kaplan. However, there is still the theoretical possibility that a third or fourth generation may exhibit stigmas traceable to such treatment. Until this is proved and until endocrine therapy accomplishes more regular and dependable results, we may well consider recommending this form of radiotherapy in properly selected cases.

DR. SAMUEL H. GEIST.—Aside from the study of the effect of the x-ray on the ovarian structure, the hormone response may also be a subject worthy of study. In the first place, what is the hormonal disturbance associated with the instances of amenorrhea and sterility? Is there a diminution or absence of the estrogenic factor or is it a gonadotropic factor which is deficient? Information of this character would possibly indicate which gland should be treated, if any.

Pituitary radiation, at least in the one case, which I had the opportunity of examining, failed to affect the histologic structure of the pituitary. This patient had received a tremendous dosage for a presumable basophilic adenoma. Of course, it is possible that physiologic activity may be disturbed without a change in the physical character of the cells. X-ray of the pituitary has been employed to relieve menopausal symptoms which are presumably due to a hypersecretion of the gonadotropic hormone. In Dr. Kaplan's case, on the other hand, x-ray of the pituitary was instituted to increase the amount of gonadotropic hormone. However, from the report tonight of 44 cases of sterility and amenorrhea of long duration successfully treated, we can assume that there is some causal relationship between the radiation and the result.

DR. JAMES A. CORSCADEN.—While it is true that an early embryo after x-ray may develop into a normal individual, something over 60 per cent will be born with mental defects. We should all be very cautious therefore about radiating any woman with an early embryo.

I suppose some statistical expert might somewhat reduce the percentage of successes reported by Dr. Kaplan, but I think from the standpoint of ordinary common sense, we must accept this as a contribution of fact.

In regard to the speculations concerning the mechanism, of the action of x-ray in these cases, the theory that seems to me most attractive is that directed toward

the corpus luteum. Anybody who uses x-ray much knows that corpus luteum cysts do disappear. We have a follow-up on about twelve hundred patients treated with sterilizing doses of x-ray or radium, the average follow-up interval being seven and a half years, that is from two years up to twenty odd years, and in not a single instance has there developed a so-called cystic ovary. There have been neoplasms of the ovary and cystadenomas, but not one follicular cyst.

DR. WILLIAM H. CARY.—I would like to ask Dr. Kaplan what are the indications for radiation to the ovary only and what for extension of the radiation to the pituitary. Furthermore, I would like to inquire if there has been any follow-up study of the radiated cases and if any subsequent disturbance of the ovary followed.

I note that in many of the patients concerning whom he gave a detailed history there was some degree of obesity. It would clarify results if we could learn whether additional exercise, diet, thyroid extract or other forms of medication were utilized during or subsequent to the x-ray treatment.

DR. FRANCIS W. SOVAK.—I have been particularly interested in one of Dr. Kaplan's cases, a young Italian woman with amenorrhea of many years' standing. She was rather obese with a low basal metabolism and was treated with thyroid extract, exercise, diet and all the kinds of endocrine therapy we knew about at that time. She was referred to Dr. Kaplan by me eight years ago, and has since been delivered of three healthy babies and her menstruation is normal, of the twenty-eight-day type.

DR. IRA I. KAPLAN.—These cases were sent to me by gynecologists or obstetricians, none by the general practitioner. I have assumed that these men carried out all the tests and examinations which they regarded as necessary to establish the indications and diagnosis. I do not establish the gynecologic reasoning for treating the patient, but use my judgment as to the method of treatment.

Dr. Healy asked if these patients were treated by other methods. Insufflation had been done in about 80 per cent of the cases. In the full text of my paper every case is reported in detail and it will be found that practically every case had the various tests which were known at that time, and the later cases had the newer methods of testing patients for functional disturbances.

We had 76 patients that improved out of 128, while 52 did not improve. Actually 14 were lost, so that we have records of only 38 cases that were failures. Seventy-six resumed menstruation, and of those there were 44 that became pregnant.

I cannot report what type of amenorrhea we were dealing with in all of these cases, whether associated with the atrophic ovary or the ovary with follicular cysts. In only one patient who was operated upon, a definitely cystic ovary was found. The adnexa were clinically always reported as being normal.

How soon after treatment do these effects occur and do we treat these cases again? Out of the entire group I think there were only two patients who had subsequent treatment. If we feel that we have failed, we do not risk further treatment after we have given three treatments over a period of three weeks. Very occasionally do we give a fourth treatment. One of the cases in which we gave a fourth treatment is one of the patients now pregnant. We believe it requires four weeks for effective menstruation to restore itself. If it does not restore itself in that time we believe treatment has failed, yet in some cases menstruation was restored even after eight weeks.

With an embryo in the uterus we do not believe radiation should be given. We do not treat even carcinoma in the presence of pregnancy, although we have had one such patient, who was later delivered of a living child. Neill has reported the same thing. Another case, before the days of the Aschheim-Zondek test, was

radiated and an abnormal fetus was born. I do not think that was due to the x-ray, although it may have been. X-ray therapy therefore does not always mean an abnormal fetus. I think the error made by the Committee which Dr. Miller referred to, was their failure to state that normal babies were born as well as abnormal ones, and that abnormal ones were born before the x-rays were ever dreamed of.

I cannot answer Dr. Geist's question about the special hormone that is lacking in these cases. All the hormone tests should be preformed, but these are carried out by the gynecologist before we get the patient. We as radiologists are simply asked to treat the case.

With regard to the pituitary, Lacassagne has shown definitely that it takes a powerful dose to destroy the glands and very little pituitary hormone is necessary to make the ovaries function. The dose we give cannot harm the pituitary.

Dr. Cary asked me to define the indications for simple ovarian radiation and for radiation of the ovary and pituitary. We select each case in accordance with personal judgment, based on a series of many cases. If we see a patient with hair on her face, with a big abdomen, thick and fat, we think she needs thyroid plus pituitary plus ovarian stimulation. If she is of short stature and, with some increased hair over the body, and a rather stupid appearance we use pituitary stimulation along with the ovarian.

With reference to subsequent disturbances, there are only two or three cases in which menstruation has again become irregular. All the others had a continuation of normal menstruation. Nine patients had more than one baby; several of them, as you saw in the slides, had three children; and even the patient with twins had two subsequent normal pregnancies.

PATHOLOGY OF THE CERVIX*

WALTER SCHILLER, M.D., VIENNA, AUSTRIA
(Clinical Pathologist, Weibel Clinic)

SOME years ago I attempted to get a general view of the results of therapy in carcinoma of the cervix cases by collecting a number of series of statistics. Since 1921 no great improvement has taken place. There is a certain slight difference in statistics of different clinics and laboratories, it is true, but the total results are almost the same. Among 100 women who come to the dispensary and clinic only 50 per cent are operable. Of this 50 per cent, we save by radiation or operation 25 per cent. Twenty-five per cent are lost.

A variation in these figures is introduced by the selection of cases regarded as operable. Brilliant operators have a higher mortality figure and a lower percentage of saved cases, while some men of lesser skill have an astoundingly high percentage of saved cases. The skillful operator's results are poor for the reason that he extends the limits of operation. The above figures mean that we generally can save only one out of four women. What can be done to improve these relatively poor statistics?

We have two methods of treatment, surgery and irradiation. The vaginal operation by Schauta and the abdominal by Wertheim give prob-

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ably the best results an operative technique can achieve. Irradiation results depend on the type and strength of the rays. Physics and not medicine must discover new rays and new methods of irradiation. Nevertheless, I do not think we can get much farther than about 30 to 32 per cent of cures by irradiation. Thus neither irradiation nor surgery may give us much improvement in the statistics of end-results.

One method of approach is left and that is early diagnosis. All statistics show that the earlier a patient is operated upon or irradiated, the greater is the probability of a permanent cure. In this belief, I decided some time ago to devote my efforts to establishing better ways of early diagnosis.

The early carcinoma and the small one are not identical. If carcinoma grew very rapidly from its onset, then a small cancer would be a young one, but that is not true. Since 1928 I have collected many very early carcinomas, and I have had the opportunity to keep a few of these cases under observation for many years. I was able to prove that in the early stage carcinoma grows very slowly. The curve of development first rises slowly, and then suddenly ascends very rapidly. This fact that carcinoma grows so very slowly at the beginning offers a marvelous chance for early diagnosis. If carcinoma's early phase lasted but a few days, it would be very difficult to get hold of early cases, but its initial phase lasts months, even two or three years or perhaps longer.

Since the expression early carcinoma is more or less accepted, we may perhaps continue to use the term. We must not forget, however, that by it we only mean a small carcinoma. In my investigations I admitted a carcinoma to be a small one if it were too small to be detected by the gynecologist with the ordinary means. For the carcinomas large enough for the gynecologist to find with the naked eye, we need not waste our time trying to find new methods.

In a monograph which Kermauner published with Schottländer on carcinoma of the cervix, he discussed the important question of how the normal epithelium and carcinoma meet one another in advanced cases. In 95 per cent of cases it is found that between the normal epithelium and the carcinoma a zone exists, occupied by neither carcinoma nor by normal epithelium. This zone Kermauner proposed to call the neutral zone or the zone of demarcation. In the remaining 5 per cent of the cases there is instead a small intermediate strip between normal epithelium and carcinoma which is characterized by two points. Under the low power it is seen that the height of this epithelium is exactly the same as that of surface epithelium, but with the high power it is clear that the cellular type is exactly the same as the cells found in carcinoma. How should we classify this strip? Should we say it is normal epithelium or should we say it is carcinoma?

Ordinarily we diagnose carcinoma only if we can demonstrate invasion. The cytologic characteristics are, however, exactly the same in

the invading ulcerating carcinoma as in this surface strip. We must decide whether the chief criterion of cancer is the cytologic characteristics or the quality of invasiveness. I prefer to decide this question from a cytologic point of view and to call this a surface carcinoma or a superficial carcinoma. Kermauner for the first time in gynecology had recognized a carcinoma that showed no point of invasion but was on the surface only.

The first step toward an earlier clinical diagnosis was to get a clearer idea of the histologic character of early carcinoma. The problem was how to obtain a number of carcinomas too small to be discovered by the naked eye. We could not expect such a carcinoma from the dispensary or from the examining gynecologist. I had at first to rely on pure chance and looked for success by examining a great number of cases. Three thousand so-called normal cervices were examined and it was thus possible not only to find a number of early carcinomas, but also to reconstruct the development of early carcinoma. I was able to divide the cases into three groups. In the first group there were three zones, first of ulceration, second of invasion, and third, what I may call carcinoma manifesting only cytologic characters. In the second group there was no ulceration and a much smaller zone of invasion, adjacent to a strip of carcinomatous epithelium. In the last group there was carcinomatous surface epithelium only, with no invasion and no ulceration, but only changes in the cytologic characteristics. This was the earliest phase of carcinoma we succeeded in recognizing, and it is doubtful if even in the future we are able to find a smaller, younger and earlier phase.

According to the old pathologists we would not be allowed to call this lesion carcinoma, for the old pathologists believed that carcinoma had to be proved by invasion. Some men use the word precancer, but this term is not well defined. Many men are using the term precancer in the sense of potential carcinoma. Others use it to imply the certainty of carcinoma in the future. It is much better to call this finding carcinoma, and characterize it as early carcinoma or still better pre-invasive carcinoma. In biopsy specimens it is not possible to rule out the possibility of invasion in the vicinity of the specimen.

To summarize to this point, two statements are to be noted. First, the early stage of carcinoma is characterized by surface epithelium that has the cytologic characteristics of carcinoma. Second, early carcinoma is identical in structure, cytology, and type of cells with the surface growth at the margins of some advanced carcinomas.

The next question was, how to make surface carcinoma visible to the gynecologists. I found that carcinoma of the cervix can be differentiated from normal epithelium in about a fifth of the cases by three characteristics. First, this zone is a little elevated. Second, the surface is not perfectly smooth and is somewhat dull. Third, while the normal

epithelium of the cervix is more or less translucent, so that the entire connective tissue with arteries, veins, and capillaries shines through and has a slightly violet or reddish tinge, the carcinomatous epithelium is opaque and whitish in color. If you describe this early carcinoma you describe it as a white patch or as a leucoplakia. About 30 per cent of all cases of beginning carcinoma gave the appearance of leucoplakia.

Leucoplakia means "white patch." It is not a pathologic entity, but simply a description, a sign, and means no more than if you say fever or jaundice or edema. These are symptoms but not pathologic entities. Similarly, we should not use leucoplakia in the sense of a clinical diagnosis. The relation between leucoplakia and carcinoma is simply that some of the young carcinomas look like leucoplakias.

What is to be done for the remaining 70 per cent of very early carcinomas that are not visible? Attempts to differentiate these carcinomas with a vital stain were unsuccessful, because it was not possible to find a dye that would stain carcinoma and not stain normal epithelium or vice versa. Now the surface layers of normal epithelium are composed of cells which appear empty when hematoxylin eosin stained, but with a special stain can be shown to be filled with glycogen. This glycogen is not analogous to the glycogen of the liver or of muscle, which is soluble in water. The glycogen of the cervix epithelium is not soluble in water, and consequently we can put the slides in water without losing part of the staining glycogen. These glycogen-filled cells are not found in carcinoma, which gives the basis for a differential test.

The method of staining glycogen is to bring it in contact with iodine. Glycogen attracts and stores iodine, and stains a deep brown. We cannot use an alcoholic solution because in that way we produce a surface necrosis, and must depend on an aqueous solution. The best solution is the so-called 1-2-3 solution, which means pure iodine 1 gm., potassium iodide 2 gm., and water 300 cm. We can transform a latent carcinoma into a visible carcinoma by using this solution, the surrounding epithelium staining brown and the carcinoma remaining perfectly white.

The iodine test serves only to discover a carcinomatous zone in a layer of normal epithelium. This test is of no value, for example, in distinguishing between ulcerating carcinoma and erosion. The differential diagnosis between these conditions has to be made by means of a biopsy.

This test, furthermore, serves only to indicate suspicious spots, but does not prove that the white spots are carcinoma. They may be carcinoma, but they may be something else. The brown stain, on the other hand, is perfectly specific, for if the surface epithelium absorbs glycogen and stains brown, it is normal. In carcinomas we see a sharply demarcated field with its central margin in nearly all cases coinciding with the junction of columnar and squamous epithelium at the external os. We never see in these beginning carcinomas a transitional zone between the white and the brown areas.

Although syphilitic leucoplakias are not rare in the mucous membrane of the mouth, they are uncommon in the cervix. In fifteen years of intensive examination of many thousands of slides of the cervix, I succeeded in discovering only three cases of syphilitic leucoplakia. Of these three, we were not perfectly sure of two. This is sufficient to prove that syphilitic leucoplakia is of no great importance.

Epithelium also loses glycogen if it develops keratinization, and this we see not very rarely. If the cervix is exposed to the air it produces horny layers, which appear as white areas of entirely different type. They are not demarcated, are distributed over the cervix, and are of a whitish or yellowish color. The carcinomatous leucoplakia does not change in appearance in a few months or even in a year's time. If you paint a cervix with keratinization two or three times at weekly intervals, you find a changing pattern—like clouds passing over the mahogany brown sky of the cervix. These confluent clouds when present are so characteristic that we rarely have to make a histologic examination.

A fourth exception is found in the fact that only the surface layer contains glycogen. If the surface layer is torn off by trauma, by the examining finger or by the speculum, we see a white area of traumatic origin. It takes a few days to store glycogen again by healing and restitution of normal conditions.

Finally there is another condition of great interest, a sharply demarcated dull white opaque area, which we may see in young individuals of twenty. A biopsy shows it to be a typical hyperkeratosis. I have carefully removed the surface epithelium in some of these cases and a week later the leucoplakia was present again. We can classify these lesions only as we do nevi or other local changes of the skin, as probably congenital abnormalities of the epithelium of the cervix. I propose for this lesion the name leucoplakia leucokeratosis, which we can prove has nothing to do with carcinoma, prolapse, or syphilis of the cervix.

It has never been proved that these cases have a tendency to change into carcinoma, and to convince myself, I have kept a certain number under observation for some years. One of these I watched for five years, another for six years, and in none was I able to find the slightest evidence of transformation into carcinoma. These cases may have a tendency to change into carcinoma, but it is not proved. We are not therefore justified in using radium, but are obliged to keep these cases under observation.

For the differential diagnosis of these types, we rely on histologic examination. For that we need not make a complete excision, for we are not interested in depth, and wish to examine only the surface epithelium. We make this removal of the surface epithelium easily with a sharp curette, elevate the edge of the epithelium and peel it off.

The incidence of carcinoma is sometimes very high and sometimes very low. The man who examines systematically all cases has a low incidence. The statistics of our dispensary show that in 100 cases there are perhaps 25 with more or less well-developed white spots. Of these 25, one can rule out 10 or 15 as being of the hyperkeratotic or traumatic type. Ten or 15 biopsies must be made and out of these one, two, and sometimes three are carcinomas. I feel satisfied if in 100 cases I find one carcinoma.

It is a mistake to carry out the test in suspicious cases only. We see carcinomas in women who never had leucorrhea, never had a discharge, in women with perfectly smooth cervices and portios. In the course of the last three or four years I have discovered a number of early carcinomas in young women who came for backache, cystitis, or some other unrelated complaint. If we could examine all women once or twice a year, by the iodine test, then we would succeed in getting all carcinomas in the initial phase and all would have a definite possibility of cure. This point seems to me of great importance.

Since 1928 I have discovered 130 cases of early carcinoma of this type. From 1928 to 1931 there were 51 cases. Of these 51, after five years 49 are alive and perfectly healthy. Two patients have died, of which one was the first case we did. This case may not have been a very early carcinoma because, in later reviewing the specimen, I found a few larger projections. The second patient we lost is a real failure from a clinical point of view, and is pathologically of special importance. This was a perfectly superficial case with almost no downgrowth. We operated upon her and two and one-half years later she developed an extensive recurrence. This one failure proves that these cases were really carcinoma. We have, however, saved 96 per cent, and we have lost only 4 per cent. The iodine test is neither painful nor difficult nor expensive. If it could be carried out systematically on all women, we could extend the probability of a 96 per cent healing to all carcinomas of the cervix.

DISCUSSION

DR. EMIL RIES.—We have been accustomed to the teaching which gives as symptoms of carcinoma, ulceration, foul discharge, cachexia, and anemia. These were considered the proper symptoms to be thought of in the diagnosis of carcinoma. Now we know these symptoms are those of the far advanced, mostly ulcerated carcinomas. We have come now to the point where we can find really early carcinoma, carcinomas that do not show ulceration. We now find carcinoma in women who never suspected it and who have no clinical signs to make them suspected of having carcinoma.

We hear much about erosion and laceration of the cervix as the causes of carcinoma. When investigators found multiplication of the epithelium they were inclined to say, here is beginning carcinoma. Others have been insisting, and I think correctly, that carcinoma is carcinoma from the beginning and that carcinoma occurs as carcinoma and nothing else. It does not arise from erosion, nor does it arise from the lacerated cervix. It occurs as carcinoma on the intact cervix that has

never been lacerated and that has never been the seat of erosion. These specimens you have seen described tonight prove to you that these cervices in which we find the earliest stages of carcinoma are not diseased cervices, but are otherwise perfectly normal cervices.

I was glad that Dr. Schiller's report showed that one patient died of carcinoma because that is proof that it was a real carcinoma. Without this death, the objection might be sustained that those cases stayed well because they did not have carcinoma.

It is interesting to compare with these results those of Hinselmann. Hinselmann had the good fortune of working in a country where the people are under great governmental control, and as a consequence serve as excellent clinical material. Every woman following labor who is entitled to sick benefits must be examined every year or oftener with the colposcope. Hinselmann collected an enormous material, and he reports also about 130 cases saved by early discovery with the colposcope. Here our propaganda about early diagnosis of carcinoma is a sad failure, and unless we can persuade the patient to come for the regular examinations which Dr. Schiller described, we shall continue to have to deal with hopeless carcinoma.

DR. HENRY SCHMITZ.—May I add a similar observation. In this instance cytologic changes were found in the amputated cervix, similar to those described by the speaker. Six months after this operation the patient returned with a bloody discharge, and on examination friable tissue was found in the left part of the cervix. Microscopic examination of this tissue showed an invasive carcinoma. At this time the case belonged to clinical Group II, that is, a doubtfully localized carcinoma. This happened about four years ago and the patient is well today.

At the time we sent the slides from the first operation to several outstanding pathologists. Half agreed with us that the cytologic changes in the amputated cervix were carcinoma, while the other half denied the existence of carcinoma on account of absence of invasiveness. The course of clinical events evidently proved that the former group was correct. It behooves us to determine now, when atypia of the cells may be diagnosed carcinoma, or at least, a transition stage from a benign inflammatory reaction to a typical carcinoma. If the observations cited by Professor Schiller and by me could be multiplied, the uncertainty could be settled. At any rate the patient should be given the benefit of the doubt and be treated for carcinoma. This may be done with radium without danger of mortality. The control of cervical carcinoma depends on the general practitioner, on his insistence to examine the patients periodically in order to exclude any possibility of abnormal tissue changes anywhere. This would mean very careful examination of the genital organs by palpation and inspection. Women should be taught to insist upon having periodic examinations when consulting a doctor.

In our statistics we have 75 cases in clinical Group I, seen up to 1931. There were 15 patients who had absolutely early and symptomless cases. These 15 patients who were treated adequately were all well at the end of five years, while in the other 60 cases which could be diagnosed clinically, the five-year mortality was about 20 per cent. This shows the importance of treating the patients when they are in the so-called pre-invasive and silent stage.

DR. FREDERICK H. FALLS.—The slow growth of carcinoma of the cervix that Dr. Schiller emphasized is very important. We have under observation now 25 patients in whom we have a negative biopsy, but a positive Schiller test. We are keeping them under close observation to determine the earliest malignant changes if and when they occur.

Will Dr. Schiller discuss the carcinoma that develops from the glands deep in the cervix beyond the columno-squamous junction? It is our impression that there

are a considerable number of carcinomas of the cervix that occur in this location. In cases of chronic cervicitis which show areas suspicious for carcinoma by the Schiller test we do a Sturmdorf operation. We split the excised cone from the internal os to the external os and stain with Lugol's solution; all suspicious areas are blocked. Usually we make eight blocks from each cone. If metaplasia is found, we make numerous sections of that block at different levels. The reason we do this is because we have seen single biopsy specimens from which six slides were taken at different levels; four were absolutely negative and two positive showing carcinoma in the invasive stage.

We have a gynecologic resident in the four large state institutions for the insane in this area. We are doing routine Schiller tests on these patients twice a year in an attempt to eliminate carcinoma from this group.

DR. CAREY CULBERTSON.—I have frequently been asked if it is necessary in every case of erosion to have a biopsy. My reply is that it is necessary to have a biopsy if you are looking for something more than you think the patient has. If you think the patient has an erosion you have a right to look for carcinoma. Without a biopsy you cannot recognize it. Dr. Schiller has emphasized the ease with which this material can be obtained. It is not necessary in every case to take off a little wedge in order to make a microscopic examination. This material will peel off like an onion skin with a sharp curette or a sharp edged scalpel.

There have been in recent years some claims by certain clinicians or pathologists that in leucoplakia we have a definite malignancy, that is, that the leucoplakia is cancerous from the beginning. Dr. Schiller has shown us very clearly why in some cases that is so and why in others that is not so.

DR. FRED L. ADAIR.—There are several possibilities that must be considered in connection with the diagnosis and cure of these cases diagnosed as early or superficial or pre-invasive carcinoma. These things have been considered in connection with other types of carcinoma, and must be considered in relation to the ultimate results of treatment of these very early cases. There is possibility, as has already been mentioned, that some of these cases may have been misdiagnosed. We must not forget that though Dr. Schiller is an expert in diagnosis, he may err in diagnosis of early carcinoma. It must be remembered that others less expert than he may make relatively frequent errors in diagnosis and that a certain number of cases which are benign will be diagnosed as carcinoma and others which are malignant will be thought to be benign. It behooves us, therefore, to be careful in accepting these microscopic diagnoses of these early lesions as infallible. Another possibility is this: It has long been known that certain cases of carcinoma may undergo spontaneous cure. If these cases are diagnosed early, there still remains the possibility that some of these very early superficial types of carcinoma may undergo spontaneous cure.

DR. H. M. MARYAN.—Dr. Schiller states that carcinoma occurs at the mucocutaneous junction, likewise Hinselmann. Yet we cannot overlook the fact that we do have glandular changes. What is the relation between the glandular changes and the superficial changes?

DR. SCHILLER (closing).—There is now no competition between the iodine painting on the one hand and the use of the colposcope on the other. Hinselmann uses both. We have only to compare the results of the iodine painting alone with iodine painting plus the colposcope. We do see most interesting details with the colposcope. But on the other hand the colposcope is expensive and heavy, and it takes a long time to learn its use. If you consider that in a dispensary like ours in Vienna we see 80 to 90 new patients in one morning, we would need five or six men

working ten hours a day merely to make colposcopic examinations of all patients. I cannot advise the country doctor or the general practitioner to use the colposcope because it is too complicated and too expensive.

Not even Hinselmann dares to make a diagnosis by the colposcope alone. When he finds suspicious areas these suspicious areas are taken out by biopsy and examined under the microscope. But by staining with iodine, we can find, likewise,[8] these suspicious areas. I believe the colposcope is very valuable for the progressive men of the profession, the specialists. I like to use the colposcope for one purpose. On one side we have the naked eye observation of the organ or the specimen, and on the other hand we have the microscopic slide. There is nothing between to make the connection between the naked eye and the microscopic picture. The use of the colposcope will combine the two. For this purpose I think the colposcope is very valuable.

Carcinoma developing from the cervical glands cannot be discovered by the iodine test. This test helps us only to discover carcinoma of the squamous cell type. Glandular carcinoma in our material of carcinomas of the uterus amounted to 2 per cent only. But I have seen carcinomatous stratified epithelium lining the cervical canal. I do not want to call this a downgrowth, because it is not invasive, it is growing along the surface. I have seen such carcinomas of the cervix extend high up, so you can realize the futility of operating on these carcinomas by low amputation of the cervix. It may happen that a small part of the surface epithelium is left. When we make an amputation of the cervix in a beginning cervical carcinoma we have to make several blocks of tissue and we have to watch most carefully to see whether the cut is within the normal epithelium or not. If we prove carcinomatous epithelium at the cut in one slide only, then we know there is the same carcinoma higher up, which will make a recurrence that has to be extirpated by a second operation or, much better, treated by radium.

Concerning the point of origin of carcinoma, I would say that cervix carcinoma begins in the area of squamous epithelium at the point where the columnar epithelium and the squamous epithelium meet each other.

Concerning the question of the further development of these initial carcinomas, we should have few opportunities to make such observations, for carcinoma once diagnosed has to be destroyed. But sometimes we fail. Such clinical failures can occur for two reasons, either the carcinoma was not diagnosed or the diagnosis was made and the patient did not come in to be operated or irradiated. I have made observations of both types. In 1922, at a time when we were not familiar with these initial findings, I made a diagnosis of suspicious epithelium. The patient was dismissed and ordered to come back in a few weeks, but did not come. Six years later, on revising my slides, I came across the old slide and now diagnosed surface carcinoma. I succeeded in getting the patient back to the hospital. I was very much astonished to see that the carcinoma had not made an extension of more than 6 or 8 millimeters. In 1929 I made a scraping from a patient, diagnosed carcinoma, and advised operation and irradiation. She refused on the ground that she felt perfectly well. A few years later I succeeded in getting her back and found that the carcinoma had increased only 2 or 3 mm. in length, with two little projections on one side and one larger projection on the other.

EXPERIMENTAL AND CLINICAL THERAPY OF VULVOVAGINAL MYCOSES*

H. Close Hesseltine, M.S., M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-In Hospital)

EVEN though certain therapeutic agents and measures may be satisfactory under given conditions, any investigation which may improve the efficacy, facility, convenience, safety, or economy of these agents or their method of administration is not only interesting but practical.

This particular study on the yeastlike fungi (monilia and cryptococci) was activated because it was often difficult or impossible for the vulvovaginal mycotic patients to return 3 to 6 times a week to receive 1 per cent aqueous gentian violet topical application, and because less frequent visits even with various kinds of daily douches at home failed many times to cure or even improve the condition. However, the results at the Chicago Lying-In Hospital and dispensary confirm the reports of Plass and his coworkers[1] when daily or bidaily treatments can be given. Many substances found unsatisfactory by other workers were not used in this study, and in general only those of the more promising nature along with a few newer and unevaluated compounds were observed in vitro. Those found promising were then tested in the presence of serum and red blood cells and against several strains of monilia. Only a few out of 84 substances were sufficiently promising by these methods to try clinically. Element iodine behavior warranted its trial. Certain problems of administration arose and now appear, partially if not completely, settled.

LITERATURE

Hesseltine and Hopkins[2] have reviewed the publications of Kolmer and Schamberg;[3] Kingery and Adkisson;[4] Kadisch;[5] Klarmann, Shternov, and Gates;[6, 7] Yi;[8] Emmons;[9] McCrea;[10] and Woodward, Kingery, and Williams.[11] There are perhaps a few other reports which might apply to the obstetric and gynecologic problem, but most of the other data is very limited and generally from uncontrolled series.

Emmons[9] and Woodward, Kingery, and Williams[11] in determining the comparative fungicidal potency of a number of chemicals demonstrated that element iodine was the best. However, these workers did not investigate many of the substances given below and furthermore confirmations were appropos. The reports of Plass, Hesseltine and Borts,[1] and of Hesseltine[12] later, contained advice that sodium bicarbonate douches were helpful, but recently Hesseltine and Noonan[13] found that

*Read before the Chicago Gynecological Society, January 15, 1937.

extreme shifts in the hydrogen ion concentration were necessary even to be fungistatic. Thus the principal value of the alkaline douche now seems to be that of a mechanical cleansing agent. The explanation for the prompt relief of symptoms, in the first twenty-four to forty-eight hours postpartum, now appears to be more likely a result in physiologic alteration rather than a change in hydrogen ion concentration in the vagina caused by the lochia. The incidence of fungi in the vagina of pregnant patients increases as pregnancy advances. Woodruff and Hesseltine[14] found 14 per cent in white lying-in patients, 33 per cent in white, and 41 per cent in colored stockyard patients.

PROCEDURE

Inasmuch as a more detailed description of this proceeding has been published by Hesseltine and Hopkins,[2] it may be stated briefly as follows:

Strain 49 *(Monilia albicans)* was arbitrarily chosen as the test organism. Actively growing 24 to 48 cultures on Sabauraud's media were transplanted into glucose broth. After eighteen to thirty hours, usually twenty-four hours, the tests were made by taking equal parts of well-suspended culture and the chemical. These were thoroughly agitated and at the five-minute interval one loopful (size 3) was transferred to a Petri dish into which Sabauraud agar was subsequently poured and the contents mixed by gentle inclination with rotation. These plates were read in forty-eight to seventy-two hours or sooner if growth appeared. The reading was made in comparison to the controls. (This is similar to F.D.A. procedure.) The chemicals were added in clinically usable concentration. Thus the final dilution was one-half this amount, yet this corresponds in part to dilution in the body. Table I includes all of the chemicals thus far tested. It may be noted that 20 of the 84 materials were sufficiently fungicidal to warrant further evaluation which is given below. Another point of importance is that alcohol and alcohol-acetone-water, both exerted definite but incomplete killing power. Throughout the study, water alone was employed as the solvent unless otherwise indicated except when only slight amounts of alkalies or some such substance were necessary to effect solubility of the compound. This illustrated very distinctly the importance of some vehicles, and this clearly indicated the necessity for adequate control in such researches. Again it was surprising to observe the ineffectiveness of some substances which have received particular recommendation for clinical use. In a few instances the test materials were examined with serum and cells present but were included in this table to show the total number of chemicals examined.

Because the cellular materials and body fluid on the vulva and in the vagina would likely decrease any drug action, human serum and red blood cells were added for tests with the more promising compounds. It is theoretically possible that some of those compounds which were not effective in vitro might behave differently in vivo but as yet there is no positive data or even suggestive evidence of it. Here one part of serum and cells (100,000 to 400,000 per c.mm.) were mixed with one-fifth part of well-laden inoculum after which one part of chemical was added (Table II). These ingredients were thoroughly mixed by shaking and after five minutes a No. 3 loopful was transferred to the Petri dish as above. The readings were made at the same time intervals. One may see at once that the fungicidal power has in

some instances been very much decreased or completely lost under these circumstances, and in not a single instance was the fungous-killing power enhanced.

TABLE I. FUNGICIDAL ACTION OF COMPOUNDS TESTED AGAINST MONILIA ALBICANS‡ (STRAIN 94)

	CONCENTRATION PER CENT	GROWTH		CONCENTRATION PER CENT	GROWTH
Other Metal Compounds					
Acetarsone (stovarsol)	2.5	++++	Potassium antimony tartrate	0.5	++++
Aluminum sulphate	2.0	+++	Potassium permanganate	0.05	++++
Argyrol	5.0	++	Silver nitrate	0.5	++++
Aurium ammonium succinimide	0.5	++++	Sodium bicarbonate	20.0	++++
Copper sulphate	2.0	+++	Sodium borate	5.0	+++
Gold chloride	0.1*	++++	Sodium perborate	0.5	++
Lead acetate	0.5	+++	Sodium ricinoleate	1.0	++++
Merthiolate	0.05	+++	Sodium salicylate	2.0	++++
Neoarsphenamine	1.0	++++	Sodium thiosulphate	4.17*	++++
Neosilvol	5.0	++++	Stannous chloride	2.0	+++
Phenylmercuric chloride	0.05	+++	Zinc sulphate	2.0	++++
Phenylmercuric nitrate	0.04*	0			
Other Compounds					
Acetaldehyde	0.75	++++	Phenol	0.5	++++
Cresol	0.5	0	Quinine dihydrochloride	5.0	++++
Formol	0.05	+++	Resorcinol	1.25	++++
Furfuraldehyde	2.0	++++	Thymol	†2.5	0
Hexylresorcinol	0.05	0	Urotropin	0.5	++++
Mercresin solution	9.0*	+++			
Vehicles					
Alcohol	47	+	Kaolin (suspension)	10	++++
Alcohol	25	+++	Potassium iodide	5	++++
Alcohol acetone water	25-5-20	++	Water (added to culture)	50	++++ (diluted only)
Glycerin	½ U.S.P.	++++			

*Tested with serum and cells present.

†Alcohol and/or other solvents used with water. Elsewhere water and broth only solvents.

‡Part of these data are taken from that of Hesseltine and Hopkins.

It is a well-known fact that any given antiseptic may not be equally effective upon even similar strains while the difference may be more pronounced with unrelated organisms and since Chlorothymol, mercuric chloride, mercuric iodide, phenyl-mercuric nitrate and element iodines still held fungicidal promise, seven other strains were selected as test organisms (Table III). These included one saccharomyces (F. 40), one cryptococcus (119), four monilia (104, 120, 155, and 156) and one endomyces* (56924). The monilial strain 155 was an atypical one with variable fermentation powers. Serum and red blood cells were used here as above. At a glance strain resistance variability is

*Obtained from Dr. W. D. Stovall, University of Wisconsin.

TABLE II. FUNGICIDAL ACTION OF COMPOUNDS TESTED AGAINST MONILIA ALBICANS (STRAIN 94)

Exposure Time 5 Min. 0 = No Growth ++++ Growth = Control

	CONCENTRATION PER CENT	GROWTH		CONCENTRATION PER CENT	GROWTH
		Acids			
Benzoic acid	†0.5	0	Pyrogallic acid	0.15	+++
Boric acid	2.0	+++	Pyroligneous acid	2.5	+++
Cinnamic acid	†1.25	++++	Salicylic acid	†0.5	0
Lactic acid	5.0	++++	Sulphosalicylic acid	0.25	++
Perchloric acid	0.05	++	Trichloracetic acid	0.05	++++
Picric acid	0.5	++++			
		Dyes			
Acriflavine	0.5	+++	Mercurochrome	5.0	++++
Brilliant green	0.5	+++	Mercurophen	0.05	0
Crystal violet	0.5	0	Metaphen	†0.25	0
Gentian violet	0.5	++++	Methylene blue	0.5	+++
Mallophene	2.0	++	Pyridium	0.5	++
		Halogens and Halogen Compounds			
Chiniofon	1.66*	+++	Mercuric chloride	0.05	0
Chloramine	0.5	0	Mercuric iodide	0.05	0
Chlorisothymol	†0.1	0	Potassium chlorate	0.25	++++
Chlorothymol	†0.1	0	Potassium iodate	5.0	++++
Dettol	2.08*	++	Sodium chloro-ortho-phenylphenate (dowicide C)	0.05	0
Diiodoquin	10.4	++++			
Iodex powder	5.0	+++	Sodium fluoride	0.5	+++
Iodine, tincture iodine	0.5	0	Sodium hypobromite	0.14	+++
Lugol's solution	0.5	0	Sodium chlorite	0.1	0
Glycerin solution (Colloid) "safety iodine"	2.0	0	Sodium iodite	0.5	+++
			Sodium tetrachlorphenate (dowicide F)	0.05	+
Iodoacetic acid	0.5	++++			
Iodokojic acid	1.0	+++			

*,†See footnotes to Table 1.

TABLE III. INFLUENCE OF HUMAN SERUM AND RED CELLS ON FUNGICIDAL ACTION OF CERTAIN COMPOUNDS WHEN TESTED AGAINST MONILIA ALBICANS (STRAIN 94)*†

Exposure Time 5 Min. 0 = No Growth ++++ Growth = Control

	CONCENTRATION PER CENT	GROWTH		CONCENTRATION PER CENT	GROWTH
Benzoic acid	0.2	++	Mercuric iodide	0.04	+
Salicylic acid	0.4	+	Sodium chloro-ortho-phenylphenate	0.1	+
Crystal violet	0.4	+			
Metaphen (tincture)	0.08	+++	Sodium hypochlorite	0.1	+
Chloramine	0.4	+++	Sodium tetrachlorphenate	0.1	++++
Chlorisothymol	0.2	++	Gold chloride	0.04	++++
Chlorothymol	0.4	0	Phenylmercuric nitrate	0.04	0
Iodine, tincture iodine	0.7	0	Sodium thiosulphate	4.17	++++
Lugol's solution	0.5	0	Cresol	0.4	+++
Glycerin solution (Colloid) "safety iodine"	0.4	+++	Hexylresorcinol	0.04	+++
	0.4	+++	Mercresin solution	9.0	+++
			Thymol	0.1	+++
Mercuric chloride	0.04	0			

*Ratio of chemical solution, serum and cells and inoculum = 1.—1. and 0.2 respectively.

†Part of these data are taken from Hesseltine and Hopkins.

conspicuous. If phenyl mercuric nitrate is precipitated by acids then conceivably its action in the vagina would be decreased. Thus, element iodine alone appeared most worthy of study as a practical therapeutical agent. Objections may be made against element iodine, because it may be irritating and even injurious to tissue in infrequent instances.

It was hoped that an iodine preparation might be found which would have the same fungicidal action as the element iodine, or possibly a compound that would liberate element iodine in a harmless manner and yet remain clinically applicable. Dr. W. J. Dieckmann[16] suggested the use of potassium iodate (KIO_3) and potassium iodide (KI). According to Peters and Van Slyke[15] $2KIO_3 + 10\ KI + 12HCl = 12\ KCl + 6H_2O + 6I_2$ (Table IV). Moreover, for each mole of element iodine one needs a mole of KI to carry the liberated I_2 in solution. This necessitates the addition of three more moles, which gives a ration of 1 potassium iodate (KIO_3) to 8 potassium iodide (KI) or molecular weight ratios of 214 to 1328 (that is 1 = 214 to 8–166), respectively. Thus, in practice for every unit weight of potassium iodate add 6.2 units weight of potassium iodide. This mixture will yield theoretically 49.3 per cent I_2 or practically one-half.

When these two halogen compounds are accordingly mixed and applied to the adult vagina, the anticipated chemical reaction is completed by the vaginal acids. Unfortunately the quick reactions were too irritating and thus as such were not practical. Since other sources of element iodine were not immediately clear, or did not seem feasible, an attempt was then made to slow up the reaction and at the same time arrange for daily treatment, most of which the patient could self-administer. Because these fungi are limited to the vagina and vulva and do not appear to invade the cervix, self-administration might be tried justifiably.

Even with the chemical behavior so well established it remained necessary to test these two chemicals individually and together as fungicides. Strain 94 was the test organism and Table V shows that both potassium iodide and potassium iodate lack any appreciable fungicidal power either with or without the addition of N/1 lactic acid. Kaolin was also tested and found to be ineffective. Potassium iodate-potassium iodide mixture (ratio 1–8 moles or 1–6.2 wt.) held no promise without acid, but with acidulation the complete killing power extended down to 1.5 per cent concentration of the mixture or 0.7 per cent I_2 equivalent. Even a 1 per cent mixture, 0.49 per cent I_2 value, had distinct but incomplete action within five minutes.

Table VI also presents additional evidence that the mixture of these two iodine compounds may have a therapeutic value because all fungi were killed in 7 other test strains (1 saccharomyces F40, 1 cryptococcus 119, and 5 monilia). The one mold growth on 155 was a contamination because it was unrelated morphologically to the test stain.

TABLE IV. TEST WITH A NUMBER OF YEASTLIKE ORGANISMS IN BROTH WITH HUMAN SERUM AND RED CELLS ADDED*

Exposure Time Five Minutes. ++++ Growth = Control.

	FINAL CONCENTRATION PER CENT	ORGANISMS TESTED						
		F40	104	119	120	155	156	56924
Chlorothymol	0.21	0	+++	++	+	0	++	0
Iodine								
Lugol's solution	1.03	0	0	0	0	0	0	0
"Safety iodine"	1.64	not run	0	0	0	0	0	0
Mercuric chloride	0.04	+	+++	++++	++	0	++	++++
Mercurophen	0.08	not run	++	0	0	0	0	+++
Phenyl mercuric nitrate	0.04	0	0	0	0	0	0	0

*From Hesseltine and Hopkins.

TABLE V

$1\ KIO_3 + 5\ KI + 6\ HCl = 6\ KCl + 3\ H_2O + 3\ I_2$.
Thus 5 moles of KI are necessary to produce the iodine and 3 additional ones are required to carry it in solution.
This gives by molar weight a ratio of 1 to 8 of KIO_3 to KI.
Since 1 molar weight KIO_3 = 214 approx. and 8 KI = (8 × 166) 1328 approx.. use by weight 1 gm. KIO_3 to 6.2 grams KI.
1 KIO_3 + 8 KI should yield 3 I_2 or about 49.3 per cent by weight.

TABLE VI. POTASSIUM IODATE AND POTASSIUM IODIDE AS FUNGICIDES AGAINST STRAIN 94 (MONILIA ALBICANS)

Exposure Time 5 Min. 0 = No Growth. ++++ = Control Growth.

	NONACIDULATED			
	CONCENTRATION %	APPROX. I_2 %		ACIDULATED
Potassium iodate	5	0	++++	++++
Potassium iodide	5	0	++++	++++
Kaolin	10 (Suspension)	0	++++	Not run
KIO_3 + KI	4	1.8	++++	0
KIO_3 + KI	2	0.9	++++	0
KIO_3 + KI	1.5	0.7	++++	0
KIO_3 + KI	1.0	0.49	++++	++

TABLE VII. POTASSIUM IODATE-POTASSIUM IODIDE MIXTURE AS A FUNGICIDE WHEN ACIDULATED* IN PRESENCE OF SERUM AND RED BLOOD CELLS WITH SEVEN OTHER STRAINS OF FUNGI

	CONCENTRATION								
Mixture %	Potential I_2	F40	119	104	120	155	156	170
(KIO_3 + 8KI) 1.5	0.7 Approx.	0	0	0	0	1 mold colony	0	0

*Acidulated with N/1 Lactic Acid
0 = No Growth ++++ = Control

The first attempt to slow up the reaction was by incorporating the iodine mixture in gelatin and glycerin suppositories. However, the acidity of the gelatin allowed the liberation of iodine on standing and thus permitted a too rapid action of the halogen when the suppository was inserted into the vagina. The second choice was kaolin (a native hydrated aluminum silicate). Because it is treated with acid for purification it is necessary to neutralize the material. This has been done by using ammonia vapor and then desiccating the kaolin to remove the excess ammonia. When sufficient dilution of the iodine compounds was made with this powder, the reaction was slowed and has given clinical results sufficiently good to encourage further observation along this general direction.

No doubt other and perhaps better methods may be revealed. It seems reasonable to believe that if the gelatin-glycerin suppositories are neutralized without leaving excess alkali that they might be satisfactory vehicles. The gelatin capsules containing the kaolin iodine

TABLE VIII. RESULTS OF IODINE AND IODINE COMPOUNDS USED IN TREATMENT OF ADULT VULVOVAGINAL MYCOSES (YEASTLIKE)

			TREATMENT		
			TYPE	WEEKS	COMMENTS
1	41750	Preg. 3rd§	*Supp. + Iod.	4	Improved, when delivered
2	46829	Preg. 3rd	Supp. + Usual	2	Improved, when delivered
3	59934	Preg. 3rd	Supp. + ½% Lys.	4	Cured
4	128488	Preg. 3rd	Supp. + Lug.	2	Cured
5	149822	Preg. 3rd	Cap. + Lug.	1	Treatment not accepted
6	158876	Preg. 3rd	Cap. + Lug.	3	Cured
7	158895	Preg. 3rd	Cap. + Lug.	1	Cured
8	159334	Preg. 3rd	Cap. + Lug.	1	Improving, thus far
9	159855	Preg. 3rd	Cap. + Lug.	1	Improving, thus far
10	159864	Preg. 3rd	‡Cap. + Lug.	1	Improved, but irritated
11	161893	Preg. 1st	Cap. + Lug.	2	Improving, thus far
12	162988	Preg. 3rd	Cap. + Lug.	1	Improving, thus far
13	St. Yd.—A	Preg. 3rd	Cap.	2	Improving, thus far
14	St. Yd.—B	Preg. 3rd	‡Cap.	3	Improving, thus far
15	St. Yd.—C	Preg. 3rd	‡Cap.	1	Improving, thus far
16	St. Yd.—D	Preg. 3rd	Cap.	1	Improving, thus far
17	St. Yd.—E	Preg. 3rd	‡Cap.	1	Improving, thus far
18	113321—1	Nonpreg.	Supp. + Iod.	2	Cured
19	113321—2†	Nonpreg.	Supp. + Iod.	2	Cured
20	136860	Nonpreg.	Supp. + I_2 + KAO.	4	Cured
21	145097—1	Nonpreg.	Supp. + Iod. Changed to Cap. + Lug.	3 2	Apparently cured
22	145097—2†	Nonpreg.	‡Cap. + Iod.	6	Cure now near
23	153228	Nonpreg.	Cap. + Iod.	2	Cured
24	161743	Nonpreg.	Cap. + Lug.	2	Cured
25	D. E.—1	Nonpreg.	Cap. + Lug.	3	Apparently cured
26	D. E.—2†	Nonpreg.	Cap. + Lug.	3	Cured

*Supp., 0.2 gm. KIO_3+KI in gelatin-glycerin suppositories.
Cap., 0.25 or 0.125 gm. KIO_3+KI in kaolin in capsule.
Iod., Iodex powder.
½% Lys., ½% lysol douche daily.
Lug., Application of diluted Lugol's solution at weekly clinic visits.
I_2+KAO., 10 to 20% element iodine in kaolin.
†Reinfection or recurrence.
‡Did not improve satisfactorily under usual treatment (gentian violet, etc.).
§Preg., Pregnancy and trimester. Nonpreg., nonpregnant.

mixture have at times given only slight indication of iodine liberation. Table VIII shows the results of those treated or still under treatment. The general procedure now in effect after establishing the diagnosis is first to gently wipe the vagina clean and then paint the entire vaginal and vulval walls with a diluted Lugol's solution. If the patient can tolerate one-fourth strength, it is used and a stronger solution used the following week, while if it irritates, greater dilution is recommended. The patient is given capsules (size 00) each containing the iodine mixture (¼ gm.) in kaolin with the direction to insert one into the vagina each evening and return in one week. Other deviations have been ⅛ gm. per 00 capsule and ¼ gm. in number 12 veterinarian. In the table a few notations indicate that iodex powder* was

*Menley and James, Ltd., voluntarily donated the iodex materials.

tried. In a series not included here it gave disappointing results. The plain iodex ointment gave some patients with vulval mycosis relief but not reliably so. Ordinarily douches should be infrequently used, if at all, while employing this procedure. If a vaginal douche must be taken, lysol or bichloride of mercury are the two most logical medicaments in the absence of free iodine, as one may observe in the foregoing tables.

Because the monilia and cryptococci can be conveyed to the genitals through fungous contamination of hands, clothes, fecal material and phallus, the patient should be instructed about the danger of reinfection. One patient in this series had a mycosis develop in the usual incubation period following a known contamination of the vulva with fecal material. The same fungi were recovered from the rectum. The fungi survive until killed off or the environment becomes unfavorable. The vaginal epithelium of women of the reproductive period and especially in pregnancy is rich in glycogen-like material which is converted into available carbohydrate substances. The constant spill of glucose over the vulva by diabetic patients produces another favorable environment for growth of fungi. The vulva and vagina of the premenacmic patient are almost never attacked and the postmenacmic individual has nearly the same freedom from fungi in the absence of diabetes.

SUMMARY AND CONCLUSIONS

Although this series is small it represents a large number of clinic patients because only those patients with sufficient symptoms to unsolicitedly complain are included. The milder ones and carriers may be treated very successfully by the usual means of gentian violet and respond quickly to the above described procedure. The severe infections and the old chronic ones may present a real therapeutic problem at times.

1. It appears that definite improvement can still be made in mycotic therapy but certainly iodine in the element form or some equally active fungicidal compound will be a part of the answer.

2. Further investigation on vehicles is recommended.

3. One per cent gentian violet is still recommended for oral thrush.

4. The fungicidal action of potassium iodate and potassium iodide, in a ratio of 1 to 6.2 gm. in the presence of an acid, has been demonstrated.

5. The preparation described and the procedure outlined has given better results so far than the dye method when less frequent visits are necessary.

6. Adequate observations are advisable to avoid tissue injury in exceptionally sensitive patients.

7. The patient should be advised about and against the possible sources of reinfection.

8. A relationship between the in vitro and in vivo experiments has been described.

The author is much indebted to Dr. Adair and all the members of his department for their cooperation. Mr. Cooke of the University Clinic Pharmacy made the capsules for clinical use.

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THE ORAL ADMINISTRATION OF PARALDEHYDE FOR RELIEF OF PAIN DURING LABOR*

Edwin J. DeCosta, M.D., and Ralph A. Reis, M.D., Chicago, Ill.

(From the Department of Obstetrics, Michael Reese Hospital)

IN CONSIDERING the management of labor from the viewpoint of pain relief, it is essential to decide at the outset just what degree of relief is to be sought, particularly with regard to the available facilities for nursing the patient. There is great danger involved in rendering a patient unconscious or even in masking her symptoms by the use of powerful agents, except in institutions in which constant medical and nursing care is available. Narcosis should not be recommended for general use since few institutions are sufficiently well regulated and staffed to warrant such routine medication. It is even debatable whether or not a state of narcosis is desirable from the viewpoint of its psychologic effect on the mother and its effect on the physiologic course of labor.

This presentation is a study of the effects of varying doses of paraldehyde on the course of labor and on the accompanying degree of analgesia and amnesia.

Paraldehyde $(CH_3CHO)_3$ was introduced by Cervello as a powerful hypnotic about fifty years ago. This polymer of acetaldehyde (CH_3CHO) is a volatile, colorless, transparent, inflammable fluid, slightly soluble

*Read before the Chicago Gynecological Society, January 15, 1937.

in water (1:8) and freely miscible with alcohol and various oils. Pharmacologically it resembles ethyl alcohol, is rapidly absorbed from mucous membranes and rapidly excreted from the body through the lungs and kidneys without damage to these organs. Its disagreeable, pungent taste and irritating effect on mucous membranes have limited its use in spite of its extremely low toxicity, absence of respiratory and cardiac depression and prompt hypnotic action.

Oral administration is distinctly preferable to rectal because of the ease of administration and the certainty and promptness of systemic action. Rectal administration during labor is not compatible with rectal examination until absorption is complete. Recent reports concern themselves only with rectal administration. This choice of the less desirable route may be based largely on the unpleasant taste of the drug.

The disagreeable taste and odor are inherent in paraldehyde. Numerous attempts have been made to mask these by incorporating paraldehyde in suitably flavored vehicles. Throat irritation can be partially relieved by dissolving the drug in a bland oil. A chilled emulsion with orange juice and oil has proved a fairly satisfactory preparation. The chief objection to disguising paraldehyde is that the total quantity administered is thereby increased and the disguise is still quite transparent. This difficulty can be overcome by giving paraldehyde in a gelatine capsule. Paraldehyde hardens gelatine and renders it insoluble in water; therefore the capsule should be filled just before use. A No. 00 capsule holds exactly 1 c.c. and is easily swallowed. The taste problem is thus satisfactorily solved but the quantity that can be given with ease is limited.

Previous investigators, with the exception of Kane and Roth, have combined paraldehyde with other drugs, particularly barbiturates, in the belief that paraldehyde itself was not analgesic. This belief may be traced to Sollmann. Most authors, when considering restlessness, ascribe it also to the adjuvant barbiturate. The accuracy of these statements will be considered in the present study.

The oral use of paraldehyde during labor was begun at Michael Reese Hospital about a year ago. This study has been empiric from the outset since neither oral dosage nor a pleasant means of administration was known. Paraldehyde was given by three methods to groups of twenty-five patients each. These patients do not represent consecutive admissions. In many, labor was too far advanced at the time of admission to permit satisfactory trial, and frequently the general maternity service was too active to allow careful nursing and observation.

An attempt was made in the preliminary group to ease the last few hours of labor by a single massive dose of paraldehyde. Four cubic centimeters were given

for each twenty pounds of body weight; this was emulsified with an equal volume of almond oil and orange juice, and chilled. Vomiting was minimized when the stomach was empty. Somnolence in the mother occurred within ten to fifteen minutes and the hypnotic effect usually lasted four to six hours.

In the second series a similar paraldehyde emulsion was given in smaller dosage. Here, response to the first dose of 15 c.c. was used as an index for subsequent medication. A second 15 c.c. dose was frequently given thirty to sixty minutes later. Usually two doses sufficed, giving relief of four to six hours' duration. Additional 8 c.c. doses were administered every two to three hours as needed, in prolonged labor.

In the third group, paraldehyde was administered in 1 c.c. gelatine capsules. The initial dose was four capsules, and this was repeated every hour until the desired hypnotic effect was secured. The maximum total quantity given was 28 c.c. during a seventeen-hour period.

TABLE I

	FIRST SERIES	SECOND SERIES	THIRD SERIES
Amnesia			
None	3	2	25
Partial	13	6	0
Complete	9	17	0
Analgesia			
Poor	2	2	10
Fair	13	5	15
Excellent	10	18	0
Response			
Excited	6	0	0
Restless	9	7	0
Quiet	10	18	25
Delivery			
Spontaneous	12	7	18
Low forceps	13	15	7
Midforceps	0	2	0
High forceps	0	1	0

The response to paraldehyde was quite different in these three groups. In Series I, where one large, almost knockout dose of 25 to 40 c.c. was given, only 40 per cent were quiet, while 36 per cent were restless and 24 per cent truly excited. Complete pain relief was obtained in 40 per cent, partial in 52 per cent, and little or none in 8 per cent. Amnesia paralleled analgesia, being complete in 36 per cent, partial in 52 per cent, and poor in 12 per cent. Twenty-eight per cent in this group vomited ten minutes to two hours after taking the medication. When vomiting occurred within one-half hour, half the preceding dose was repeated. The average duration of labor was sixteen hours, thirty-four minutes, and the average length of labor after paraldehyde was given was five hours and two minutes. Spontaneous delivery occurred in 48 per cent; low forceps were used in 52 per cent.

The second series was more encouraging. The average individual dose was only 15 c.c. but the total dosage frequently reached 45 c.c. Seventy-two per cent were quiet, 28 per cent restless and none excited. Analgesia was excellent in 72 per cent, fair in 20 per cent, and poor in 8 per cent, while amnesia was complete in 68 per cent, partial in 24 per cent, and absent in 8 per cent. Vomiting occurred more frequently, being present in 48 per cent. The total duration of labor averaged nineteen hours, thirty-seven minutes, while the average time following the last dose of paraldehyde until delivery was four hours, forty-one minutes.

TABLE II

	FIRST SERIES	SECOND SERIES	THIRD SERIES
Hours of labor (total)	16°34′	19°37′	13°20′
Primiparas	17°21′	19°56′	13°40′
Multiparas	10°45′	17°13′	12°23′
Before paraldehyde was given	11°32′	11°39′	7°54′
Primiparas	12°06′	11°55′	8°06′
Multiparas	7°35′	9°43′	7°07′
After last dose of paraldehyde	5°02′	4°41′	2°11′
Primiparas	5°15′	4°29′	2°42′
Multiparas	3°10′	6°10′	52′

There appeared to be a marked variation in the individual response to the emulsion. With some patients, a single dose, containing 15 c.c. of paraldehyde, was sufficient to give complete amnesia and excellent analgesia for several hours, while with others three doses had little or no effect in relieving pain or inducing forgetfulness. The larger and more obese patients reacted less favorably. Being readily soluble in oil, paraldehyde may be dissolved in the body fat and removed from the circulation. The occasional stimulation that occurs with the barbiturates was not observed in the second group of patients. Restlessness was seen only at the acme of the contraction, and the patient relaxed and dropped off to sleep again as the pain subsided.

The constant attention that these patients required to prevent injury to themselves and the difficulty of maintaining asepsis during delivery prompted the investigation of the effect of smaller doses in which it was the aim to have a conscious patient who rested well between contractions. It would be possible to apply such a technique to other than hospital confinements.

The results of this investigation indicate that in small doses paraldehyde is not an amnesic and only a fair analgesic, but is an excellent hypnotic. Patients who have received these small doses sleep or doze between pains but are wide-awake and in complete contact with their environment during the contraction. There is no danger of falling out of bed or breaking an arm over the side board. Such patients are much more quiet during the contraction, whimpering softly but never excited. When questioned following delivery, the response is characteristically the same: that the medication seemed to make the contractions stronger and more frequent and yet more bearable, and that between pains they fell asleep. In this series, labors were short and low forceps were employed in only 28 per cent, the other 72 per cent delivering spontaneously.

Paraldehyde appears equally suitable for use in primiparous and multiparous women. At the outset of this study, it seemed important carefully to individualize the patient with regard to parity, stage of cervical dilatation, strength and frequency of contractions, and condition of the membranes. On this basis, medication was withheld until the primiparous cervix had reached approximately 5 cm. dilata-

tion and forceful contractions recurred at three-minute intervals. These criteria were of little aid in managing the labor and finally were dropped, paraldehyde being given when the patient was actively in labor and complaining of painful contractions, without regard to the cervix, membranes, or parity.

The threshold of pain appreciation is in itself most variable. Some investigators believe that a normal labor is relatively painless, and that discomfort arises from psychic stimuli, especially fear. These stimuli are supposed to act through the sympathetic nervous system causing constriction of the circular fibers of the uterus, increasing the resistance to dilatation. This prolongs labor and increases pain perception. There is clinical evidence that an element of truth may be present in the foregoing. Fear, anxiety, and worry are known to cause spasticity in other organs containing unstriped muscle. Abnormal conditions in these organs frequently are cured by suggestion and faith. So too during labor, the calm, relaxed patient who has faith in her physician frequently has a rapid, more or less painless delivery; while the tense, fearful patient drags on for hours with no apparent reason for delay. It has long been observed that certain physicians enjoy success with a procedure that fails in the hands of others, that one person administering an analgesic gets better results than another, and that cultists succeed where doctors have failed. How else can we explain these facts unless we accept the influence of the mind over bodily function? Perhaps it is in this respect that paraldehyde in small doses seems so efficacious—it aids the patient to relax and labor follows a more normal course, less influenced by the untoward stimuli that may arise from lay misconceptions of the normal process of delivery.

As shown by Moore and McCurdy, and Kane and Roth, paraldehyde in 30 to 40 c.c. doses did not significantly change the frequency or strength of uterine contractions. In this series, when small individual doses were used, contractions seemed stronger and more frequent.

With all three methods of medication, the pulse, respiration, blood pressure, and urinary findings were unchanged. There was no evidence of increased postpartum bleeding. There was no maternal mortality, and following the standard of the American College of Surgeons the maternal morbidity was 2.6 per cent.

The odor of paraldehyde can be detected in both liquor amnii and maternal blood. It is likewise detectable on the breath of mother and baby for at least twenty-four hours. Fetal apnea was observed in six babies, all of whom began to breathe and cry as soon as mucus was removed from the larynx.

One baby died. This child was six weeks premature, weighed 2035 gm., and was delivered by low forceps and episiotomy after a seven-hour, five-minute labor.

The mother, a primipara, received two 15 c.c. doses of paraldehyde in emulsion one hour apart, vomiting forty minutes after the first dose, and was delivered one hour, thirty minutes after the second. The baby died one hour after delivery and on postmortem examination a diagnosis of atelectasis was made.

TABLE III

	FIRST SERIES	SECOND SERIES	THIRD SERIES
Age			
Primiparas	22.7	24.1	20.3
Multiparas	32	28.7	28.0
Weight of patient			
Primiparas	148.6	142.9	146.7
Multiparas	130.7	147.3	155.6
Weight of fetus			
Primiparas	3290	3075	3273
Multiparas	3400	3708	3792
Fetal morbidity			
Tracheal catheter	1	3	0
Fetal mortality	0	1	0

DISCUSSION

Paraldehyde in large doses possesses both analgesic and amnesic properties. Large oral doses, however, are difficult to administer and frequently lead to vomiting. In addition, it causes a very definite percentage of restlessness and occasionally excitement at the acme of contraction. In smaller doses, paraldehyde is not an amnesic, and only a fair analgesic but is an excellent hypnotic and definitely seems to shorten the course of normal labor. Oral administration is highly desirable because it insures prompt and certain action. The unpleasant taste, smell and irritating effects can be avoided by the use of gelatin capsules. Paraldehyde is not advocated as a substitute for ethylene or ether, but as a valuable adjunct to either during the first and early second stages of labor. It is a stable, safe, inexpensive, readily procurable drug, requiring neither special equipment nor technique. In doses of 4 c.c. repeated at hourly intervals, special nursing is not necessary. With this dosage there is no increase in operative interference.

SUMMARY

1. The therapeutic value of paraldehyde given orally to patients in active labor has been investigated.

2. For convenience, these patients have been divided into three groups of twenty-five patients each; in each group the technique was varied.

3. Paraldehyde given in small doses of 4 c.c. every hour in gelatin capsules does not render the patient amnesic, is sometimes mildly analgesic, but is definitely sedative. In these doses it does not cause restlessness and seems to expedite delivery.

4. As far as is known, paraldehyde is absolutely safe to the parturient patient and fetus in the varying dosages used in this study.

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DISCUSSION

DR. RALPH A. REIS.—The advantage of paraldehyde is that with 4 c.c. doses we have kept the patients more quiet over longer periods of time than we have been able to do with either barbiturates or morphine. The objection we have had to barbiturates has been the necessity for constant nursing. This limits the use of barbiturates.

Paraldehyde is given early, repeated hourly, and the patient is quieted. We believe that by gradually increasing this minimum we will find the proper dose of paraldehyde for institution use and for the general practitioner who is conducting home deliveries. We think this will be an excellent method of keeping our patients under continuous sedation without producing any harmful effects on mother or fetus. We do not continue paraldehyde after ethylene analgesia has been started, although we have continued its use through a good part of the second stage.

DR. J. DUANE MILLER, Grand Rapids, Mich.—I would like to ask some questions and I would like to report one death. Dr. DeCosta said the drug has a low toxicity, but just exactly how low is that toxicity? What is the variability in susceptibility to this drug?

Dr. Alexander M. Campbell and I within the past year, saw a patient in consultation who had been perfectly normal throughout her pregnancy. She went into labor spontaneously and was given a standard dose (6 drachms) of paraldehyde by rectum. She went into shock and the blood pressure went so low it could scarcely be taken. The patient lived approximately twenty-three hours; the fetus died shortly after the accident occurred. An autopsy was done which showed cloudy swelling of parenchymatous organs and blood destruction. It apparently was a death from the paraldehyde. It is said that the dose was checked carefully and was correct.

DR. C. E. GALLOWAY, Evanston.—This paper is based on 75 cases, 25 in each series. I would like to know what the experience has been with the continued, routine use of the drug.

We have given barbiturates in a little over 2300 cases, and the maternal mortality and fetal mortality have been increased. Before we can make any definite conclusion about any drug it must be used over a considerable period of time and in a considerable number of cases.

This whole question comes down to one point: in the particular labor that one is conducting, is it advisable to attempt to relieve the pain of labor? There

are plenty of cases in which one does not care to attempt it. When you decide that a case does need relief the question remains of what we are to use. I think we should attempt to work out this problem gradually and carefully.

DR. JOSEPH L. BAER.—A medicolegal angle is involved in the use of potent agents in the course of labor. You have heard why we have abandoned the routine use of the barbiturates. A woman subjected to certain drugs may become restless and sustain real injuries unless she is closely guarded and protected. The institution and the physician are responsible for that patient. That is why our superintendent, in discussion with our department, took the position that unless the patient is specially nursed she should not have a drug that might lead to serious trauma.

Special nursing is again a relative matter. The mere fact that a special nurse is engaged for a patient for eight hours does not necessarily mean that that special nurse is continuously at the bedside of that patient. It is conceivable that the special nurse may leave the patient for three minutes and in her absence something of serious moment happens to that patient. We have improvised side boards for our labor beds, but it has happened in our hospital that the patients have gotten over the side boards and out of bed, and it is readily understandable that this might result in a serious accident. Continuous special nursing must be really continuous to be adequate medicolegally.

DR. DeCOSTA (closing).—The only reference in the past decade to fatal termination was one by MacFall in the *British Medical Journal* in 1925, in which he reports a paraldehyde addict who committed suicide by drinking at least three ounces. He quotes two previous deaths of which he knew and they both occurred before 1900; one of these was a suicide, the other associated with typhoid fever.

So far as unusual susceptibility is concerned, we have not seen it in this small series. We have seen patients who were resistant to its action and one patient particularly, a doctor's wife, who received little or no benefit from 45 c.c.

We have run more than the 75 patients reported, but some were deleted from the present report, because they had received insufficient medication. There was also an additional series of twenty patients who received 6 c.c. of paraldehyde in capsules at hourly intervals and gr. ⅙ morphine sulfate. The morphine usually accompanied the second dose of paraldehyde. This series was omitted because we were anxious to report the response to paraldehyde alone. With morphine there was better analgesia and amnesia and the advantages of small doses of paraldehyde were retained. At present we are employing this technique with satisfaction, and plan to discuss it in greater detail in a subsequent communication.

Waters, E. G.: Bleeding in Late Pregnancy, Am. J. Surg. **30**: 444, 1935.

Placenta previa, ablatio placentae and rupture of the uterus constitute the most life-endangering causes of late pregnancy bleeding. The hemorrhage and/or shock associated produce profound alterations in the normal physiologic adjustment of the body. Depletion of blood volume and change of blood distribution are the primary factors in the development of the severe clinical conditions. Blood replacement by transfusion is an essential element in treatment. A series of cases occurring in 14,000 deliveries is reported.

J. THORNWELL WITHERSPOON.

HEART DISEASE IN PREGNANCY*

An Analysis of 110 Cases

Arthur E. Lamb, B.S., M.D., Brooklyn, N. Y.

(From the Prenatal Cardiac Clinic and the Wards of the Brooklyn Hospital.)

THE functional classification for cardiac patients accepted by the American Heart Association was first applied to pregnant women with heart disease by H. E. B. Pardee[1] in 1922. Since the publication of this paper it has become generally accepted by most workers in this field as a guide in the ability of cardiac patients to withstand pregnancy and labor. Carr and Hamilton[2] in 1934 took exception to the use of the functional classification.

In 1934 a preliminary report[3] was published from the prenatal cardiac clinic of The Brooklyn Hospital. In this report the functional classification for cardiac patients was used in evaluating pregnancy risks, and it was found that some of the women who would be considered excellent subjects for pregnancy and labor on the basis of this functional classification alone, stood the test of pregnancy badly. On account of this it was suggested that other factors should be considered.

This report is based on an analysis of the cases studied in the prenatal cardiac clinic and on the wards of The Brooklyn Hospital over a nine-year period from July, 1926, to July, 1935.

Since 1926, there has been a close cooperation between the obstetric and medical departments. A woman entering the obstetric clinic for prenatal care has her heart examined by the obstetrician on her first visit, and if the slightest abnormality is detected she is referred to the cardiac clinic where, after a careful history and a thorough physical examination of the heart, an electrocardiograph and an orthodiagram or a six-foot roentgen-ray are obtained. The forms of the New York Heart Association are used. This complete study is necessary to differentiate functional or adventitious murmurs from those of organic disease.

Functional murmurs are systolic in time and may be heard at any of the valvular areas. They are not associated with any change in size or contour of the heart. In addition there is no history of previous rheumatic infection. Women with these murmurs have been followed over this ten-year period and not a single instance of cardiac insufficiency developing during pregnancy or labor has been encountered. As noted in our preliminary report,[3] a good proportion of these *bruits* disappear following delivery. A detailed analysis of this matter will be reported

*Read at the Scientific Meeting of the Committee of the Cardiac Clinic of the New York Heart Association, April 28, 1936, and before the Brooklyn Gynecological Society at The Brooklyn Hospital, October 3, 1936.

in a separate paper. The recognition and separation of these cases from those presenting organic lesions is one of great importance for their inclusion in such study as this would so markedly reduce the heart failure and death rate as to give an entirely erroneous impression of the problem of pregnancy in the cardiac patient. As far as can be determined only patients suffering from organic disease of the heart are included in this report. Only those cases are accepted as having organic disease as determined by the criteria[4] adopted by the New York Heart Association.

There were 110 cases of organic heart disease among the 5,366 admissions to the obstetric clinic from July, 1926, to July, 1935 (Table I). These were discovered

TABLE I. ANALYSIS OF PREGNANT CARDIAC CASES

Admitted to Obstetrical Clinic, July, 1926 to July, 1935	5366
Referred to Cardiac Clinic	367
Functional cardiac murmurs	257
Organic heart disease	110
Incidence of heart murmur in pregnant women	6.8%
Incidence of functional murmurs in pregnant women	4.8%
Incidence of organic heart disease in pregnant women	2.06%

among 367 patients referred to the cardiac clinic. The remainder, 257, had functional murmurs. The total incidence of heart murmurs in pregnant women was 6.8 per cent. Of these 4.8 per cent were of the functional type, 2.06 per cent represented organic disease. Sparks,[5] from a survey of the literature up to 1929, reports an incidence of organic disease from 0.25 to 2.8 per cent. The more recent reports[6-8] vary from 0.66 per cent to 4.15 per cent.

The 110 cases here reported were separated according to etiology (Table II); 102 were rheumatic, three were congenital, three were arteriosclerotic, while in two the

TABLE II. ORGANIC HEART DISEASE—ETIOLOGY

*Rheumatic	102
Congenital pulmonary stenosis	3
Arteriosclerotic	3
Etiology unknown cardiac hypertrophy	2
92.7 per cent of heart disease in pregnancy—rheumatic	

*In our preliminary report there was one case reported as syphilitic heart disease, and the finding of aortic insufficiency associated with a positive Wassermann during pregnancy. Subsequent negative Wassermann reactions and the finding of a presystolic murmur at the apex caused us to reclassify this case as rheumatic.

Since this paper was written, this patient died and autopsy revealed a syphilitic aortitis and aortic insufficiency. So the case should be reclassified as syphilitic disease of the heart, and consequently the incidence of rheumatic disease of the heart should be 91.8 per cent instead of 92.7 per cent.

etiology could not be determined. Of the heart disease encountered in this series 92.7 per cent was rheumatic. Carr and Hamilton[2] in a series of 500 patients report an incidence of 94.4 per cent. Among the rheumatic group, the valvular lesions encountered are shown on Table III. Mitral stenosis with or without mitral insufficiency was most frequent, occurring in 74.5 per cent. Carr and Hamilton[2] report the incidence of mitral stenosis to be 77 per cent; 80 per cent of their patients had mitral involvement while 100 per cent of this series had a mitral lesion. There were 13 women with mitral insufficiency. This diagnosis was made when a systolic murmur was found at the apex, together with definite changes in the size and contour of the heart on x-ray examination, and when a definite history of rheumatic

TABLE III. VALVULAR LESIONS ENCOUNTERED IN RHEUMATIC HEART DISEASE

VALVULAR LESIONS	CASES	PERCENTAGE
Mitral insufficiency	13	12.7
Mitral stenosis with and without mitral insufficiency	76	74.5
Aortic insufficiency with mitral stenosis and insufficiency	10	9.8
Aortic stenosis and insufficiency with mitral stenosis and insufficiency	2	2.0
Triscuspid stenosis with mitral stenosis and insufficiency	1	1.0

Mitral valve involved in 100 per cent.
Mitral stenosis with and without mitral insufficiency occurred in 89.
Percentage—87

fever was obtained; patients with a systolic murmur at the apex and a rheumatic history but with a normal cardiac silhouette were excluded. These rigid criteria should be fulfilled in order to avoid the inclusion of cases of functional systolic murmur.

On referring to Table IV, it is seen that no instance of decompensation was encountered with mitral insufficiency alone. There were 76 women who had definite mitral stenosis. Of the 106 pregnancies in these women heart failure occurred during 27 of them. Mitral stenosis was also found as the sole lesion in 5 out of 9 patients who died. Conclusions as to the incidence of failure and death in other lesions could not be drawn on account of the small number of cases. It is of the utmost im-

TABLE IV. RELATION OF VALVULAR LESIONS TO MORBIDITY AND MORTALITY

LESIONS	NO.	PREGNANCIES	DECOMP.	PER CENT DECOMP.	DEATHS	
					TOTAL	PRENATAL CARE
Mitral insufficiency	13	15	0		0	0
Mitral stenosis with and without mitral insufficiency	76	106	27	25	5	2
Aortic insufficiency with mitral stenosis and insufficiency	10	13	3		2	0
Aortic stenosis and insufficiency with mitral stenosis and insufficiency	2	3	2		0	0
Triscuspid stenosis with mitral stenosis and insufficiency	1	1	0		0	0
Congenital pulmonary stenosis	3	4	3		1	1
Arteriosclerotic heart disease	3	3	1		1	0
Etiology unknown cardiac hypertrophy	2	5	0		0	0
Totals	110	150	36		9	3

Two cases not confined in The Brooklyn Hospital.

Decompensated	24.0%
Mortality	8.2%
Mortality of cases studied and treated in prenatal cardiac clinic.	2.7%

portance, therefore, to differentiate between insufficiency and stenosis of the mitral valve because the former is a relatively benign lesion while the latter is an extremely grave complication of pregnancy.

The only congenital lesion encountered was pulmonary stenosis, and decompensation occurred in three of the four pregnancies.

Nine deaths occurred in this series of 110 patients, a total mortality of 8.2 per cent. Most of these deaths were in women who were admitted directly to the wards in acute decompensation and who had not been supervised in the cardiac clinic. There were only three deaths among the women who had had prenatal care, or a mortality of 2.7 per cent. In our preliminary report the mortality among patients treated in the cardiac clinic was 2.2 per cent, while in the untreated cases it was 20 per cent. The necessity of careful prenatal supervision is obvious.

It has been demonstrated by Carr and Hamilton[2] that there is a direct relationship between the age of the patient and the incidence of decompensation. Thirty-five per cent of their patients decompensated at the age of thirty-five. A chart (Fig. 1) has been prepared in which the patients in this series are grouped according to

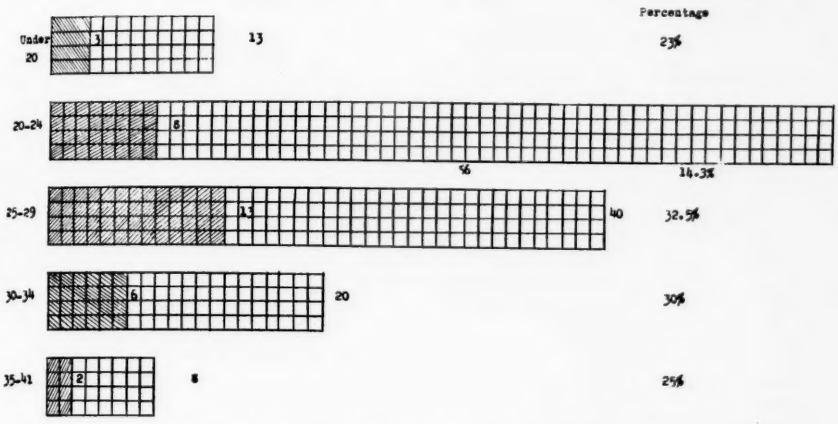

Fig. 1.—Rheumatic heart disease. Relation of age of patient to decompensation.

age. An increasing percentage of decompensation occurred up to the age of twenty-nine. The number of cases in the age group above twenty-nine years is small and an increasing percentage of failures cannot be shown.

The chart (Fig. 2) shows that there is an increasing percentage of failures with each subsequent pregnancy. Eighty per cent of the patients that returned for the fourth pregnancy developed signs of heart failure and of those that had over four pregnancies, 60 per cent failed. Two patients in this latter group had arteriosclerotic heart disease and did not decompensate, so actually there were 75 per cent of the rheumatic cases that failed. Therefore, 75 to 80 per cent of patients with rheumatic heart disease cannot tolerate more than three pregnancies.

In the preliminary report,[3] a relationship between the month of pregnancy and the onset of decompensation could not be demonstrated, probably because the series was then small. In this study, as one would expect, the greatest number of decompensations occurred in the latter months of gestation (Fig. 3). As pregnancy advances there is a gradual increasing burden on the heart due to the increasing cardiac output. Stander[9] has shown in normal gestation in animals and human

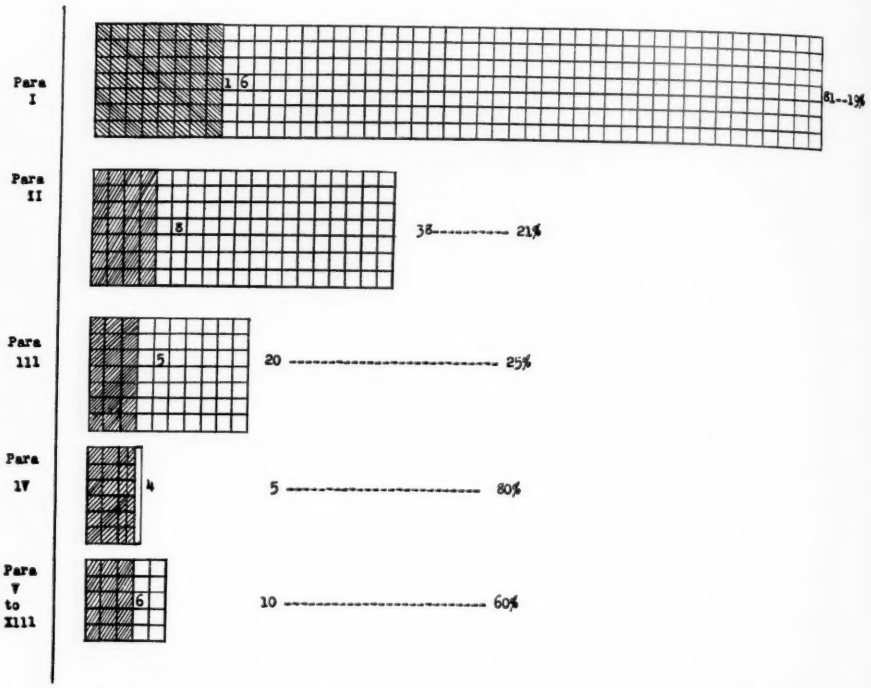

Fig. 2.—Relation of parity to decompensation; 154 pregnancies (4 pregnancies before admission to Cardiac Clinic). Two patients with arteriosclerotic heart disease did not decompensate, one para vii and one para xii.

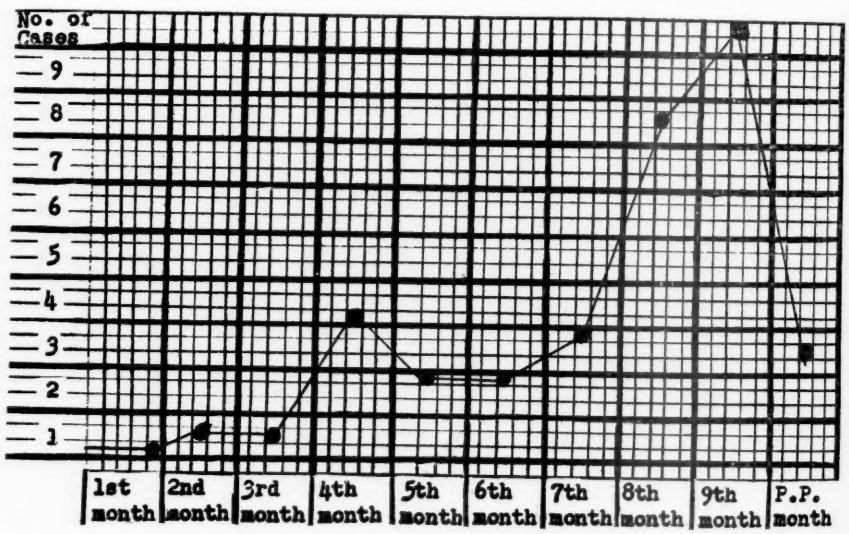

Fig. 3.—Rheumatic heart disease. Relation of months of pregnancy to decompensation.

beings that the cardiac output rises above the normal level early in the fourth month and steadily increases until at term it amounts to approximately 50 per cent above normal. This is of importance because if a patient decompensates early in pregnancy, the likelihood of another breakdown in the latter months of gestation is greater because of the increased cardiac strain existing at that time.

In most clinics today, the functional classification for cardiac patients accepted by the American Heart Association is used as an index of whether women with heart disease will be able to withstand the strain of pregnancy and labor. Cases are, therefore, grouped according to the ability of the heart to withstand effort, rather than according to the structural damage and other factors.

The following classification is used: Class 1, patients with organic heart disease able to carry on ordinary physical activity without discomfort. Class 2, patients with organic heart disease unable to carry on ordinary physical activity without discomfort: (A) activity slightly limited, and (B) activity greatly limited. Class 3, patients with organic heart disease and with symptoms or signs of heart failure at rest, unable to carry on any physical activity without discomfort. Pardee[10] after studying the reaction of 106 pregnant cardiac patients to an exercise test concluded that Class 1 patients will not be expected to give trouble from cardiac insufficiency. Class 2A patients probably will not give trouble, but there is a fair chance that a Class 2B patient will decompensate. The Class 3 patients were not subjected to the test, as they were already decompensated, and he found their management difficult and the mortality high.

TABLE V. FUNCTIONAL CLASSIFICATION

LESION	NO. OF CASES	NO. OF PREGNANCIES	CLASS 1		CLASS 2A		CLASS 2B		CLASS 3	
			NO FAILURE	FAILURE	NO FAILURE	FAILURE	NO FAILURE	FAILURE	FAILURE	
Mitral insufficiency	13	15	7	0	8	0	0	0	0	
Mitral stenosis with and without M. I.	76	106	38	5	39	6	2	7	9	
Aortic insufficiency with M. S. and M. I.	10	13	3	0	6	1	1	1	1	
Aortic stenosis with M. S. and M. I.	2	3	0	0	1	0	0	0	2	
Triscuspid stenosis with M. S. and insufficiency	1	1	0	0	1	0	0	0	0	
Congenital pulmonary stenosis	3	4	0	1	1	0	0	0	2	
Arteriosclerotic heart disease	3	3	0	0	1	0	1	1	0	
Cardiac hypertrophy etiology unknown	2	5	0	0	5	0	0	0	0	
Total	110	150	48	6	62	7	4	9	14	Total
Number decompensated				6		7		9	14	36
Per cent decompensated				11%		10%		69.2%	100%	24%
Deaths				2				2	5	9

While the patients in this series were all classified functionally, they were not subjected to an exercise test. Reliance was placed on their ability to carry on the usual exertions and strains of life. If upon questioning there were no symptoms suggesting the slightest evidence of cardiac strain, they were placed in Class 1. The others were grouped accordingly. The number of patients in each functional group at the time of the examination is indicated in Table II. Eleven per cent of Class 1 patients, 10 per cent of Class 2A patients, and 69.2 per cent of Class 2B patients developed signs of cardiac insufficiency. The functional classification is therefore helpful in selecting pregnancy risks, so far as it indicates that women in Class 2B do not tolerate pregnancy well. If a patient is in Class 1 or Class 2A, it is no guarantee that she will pass through pregnancy and labor without development of cardiac insufficiency.

There are additional factors that must be considered to make a more accurate prognosis. These are:

First: The structural changes in the heart. These have been judged by the size of the heart and the extent of the valvular damage.
Second: The duration of the disease.
Third: The presence of signs indicating activity of the rheumatic process.
Fourth: The presence of auricular fibrillation.

1. *Structural Changes in the Heart.*—In 79 women the relationship of the total diameter of the heart to the transverse diameter of the chest has been studied. Table VI shows that the larger the heart in relation to the transverse diameter of the chest, the greater the danger of failure. Where the total diameter of the heart exceeded 55 per cent of the diameter of the chest, decompensation occurred in 50 per cent. When it was in excess of 60 per cent, 78 per cent failed, and when 65 per cent, they all decompensated. The larger the heart the greater danger of cardiac insufficiency.

TABLE VI. 79 CASES IN WHICH RELATIONSHIP OF SIZE OF HEART TO TRANSVERSE DIAMETER OF CHEST WAS OBTAINED

CARDIOTHORACIC RATIO	NO. OF CASES	DECOMP.	DIED	PER CENT DECOMP.
Less than 0.450	3	0	0	0
0.451-0.500	25	5	3	20%
0.501-0.550	21	5	0	24%
0.551-0.600	16	8	2	50%
0.601-0.650	9	7	4	78%
0.651-0.700	3	3	1	100%
0.701-0.750	2	2	1	100%
	79	30	11*	

*2 patients died. One four years and one eight years following pregnancy. The other nine died during pregnancy.

The extent of the valvular damage was determined by an analysis of the murmurs present. Table VII shows the relationship of the murmurs found to decompensation. None of the patients who presented only a systolic murmur at the apex gave trouble during pregnancy. Where a short presystolic or an early diastolic murmur occurred 15 per cent decompensated, but when in addition to the presystolic or early diastolic murmur, an aortic or tricuspid lesion was present, the number of failures rose to 28 per cent. A long rumbling diastolic murmur at the apex, existing throughout diastolic, definitely increased the risk. Sixty-two per cent of these women decompensated. When this murmur was discovered, together with an aortic lesion, about the same percentage failed. The finding of this type of murmur at the apex is indicative of a high degree of structural damage of the mitral valve. Upon four of these patients postmortem examinations were secured, and they showed a high degree of mitral stenosis.

TABLE VII. RELATION OF ANATOMIC LESION TO DECOMPENSATION AND DEATH. BASED ON ANALYSIS OF MURMURS

	NUMBER OF CASES	NUMBER OF DECOMP.	PER CENT OF DECOMP.	DEATHS	POST-MORTEM
Systolic at apex	13	0	0	0	
Presystolic or short diastolic at apex	45	7	15	3	
Presystolic or short diastolic at apex associated with aortic lesions and triscuspid	7	2	28	1	
Long diastolic at apex filling diastolic	32	20	62	8	4
Long diastolic associated with aortic lesion	5	3	60	1	
Totals	102	32		13	4

CASE 35173.—The heart was found to be normal in size. The mitral valve was stenotic, admitting the tip of only one finger.

CASE 15735.—The heart weighed 400 gm. Mitral valve markedly stenotic; does not admit the tip of the fifth finger. Mitral slit 1 cm. by 0.5 cm. in diameter.

CASE 57725.—The heart weighed 700 gm. The mitral valve admits the tip of one finger. The edges of cusps were rounded and thickened. The chordae tendinae were shortened, thickened, white, and fibrotic.

CASE 15005.—The heart was normal in size. The mitral orifice was funnel-shaped and narrow. The opening was about 4 by 7 mm. The valve cusps were thickened and coherent. The upper lobe of the right lung was completely consolidated. The left lung was moderately consolidated throughout. The patient died of lobar pneumonia.

There is a definite relationship between the extent of the structural damage in the heart and decompensation: no matter what the functional classification may be, if the size of the heart is more than 55 per cent of the total diameter of the chest or if the patient presents a long rumbling diastolic murmur at the apex the likelihood of cardiac insuffi-

ciency developing during pregnancy is great. In order to examine the accuracy of these statements the patients in Class 1 and 2A that decompensated were analyzed according to the size of the heart and the presence of a long diastolic murmur at the apex. All but one of these patients showed either one or both of these signs (Table VIII).

TABLE VIII. ANALYSIS OF CLASS 1 AND 2A. PATIENTS THAT DECOMPENSATED ACCORDING TO EXTENT OF VALVULAR LESION

UNIT NO.	FUNCT. CLASS	SIZE OF HEART	LONG RUMBLING DIASTOLIC AT APEX	DIAG.
14416	1	0.594	No	M. S.
43101	1	0.457	Yes	M. S.
32506	1	0.635	No	M. S. M. I.
57675	1	0.591	Yes	M. S. M. I.
19162	1		Yes	M. S. M. I.
47837	2A	0.599	No	M. S.
12210	2A	0.500	No	M. S.
45272	2A	0.497	Yes	M. S.
34701	2A	0.537	Yes	M. S. M. I.
19360	2A	0.626	Yes	M. S. M. I.
51905	2A	0.584	Yes	M. S. M. I.
12282	2A	0.576	Yes	M. S. M. I.

Size of Heart less than 0.501—3 patients
Size of Heart from 0.501-0.550—1 patient
0.551-0.600—5 patients (Heart size above 0.551—7 or 63 per cent)
Number with long rumbling diastolic murmur 9 or 75 per cent.
There was only one patient in series who had neither a long rumbling diastolic murmur or heart size under 0.550 or 92 per cent showed with one or other sign.

TABLE IX. ACTIVE RHEUMATIC FEVER OR CHOREA DURING PREGNANCY

	NO. OF PATIENTS	NO. DECOMP.	DEATHS
Active rheumatic fever	4	2	0
Chorea	3	2	2

Ages of patients varied from 18-22 years with one exception age 35

Rheumatic Cases	102
Active Rheumatic Cases	7
Percentage Activity	6.8%

2. *The Duration of the Disease in Rheumatic Cases.*—There were 66 patients in whom a definite history of the onset of the rheumatic infection was obtained, and the duration of the disease was computed. Fig. 4 shows that in 10 patients who had rheumatic heart disease of less than five years' duration, 20 per cent decompensated. In this group we encountered patients with the signs of activity of the rheumatic process. This we will show later influenced the incidence of decompensation in this group. Twenty-six per cent failed who had

rheumatic heart disease of from six to ten years' duration decompensated. The number of instances of duration of disease exceeding twenty years is too small and no accurate conclusion can be drawn. Generally speaking, the longer the duration of the disease the greater the possibility of failure developing during pregnancy.

3. *Activity of Rheumatic Process.*—When women with rheumatic heart disease reach the childbearing age, most of them no longer present evidences of activity of the rheumatic process. Only 7 showed signs of acute rheumatic fever or chorea during pregnancy, an incidence of 6.8 per cent. Of the four with rheumatic fever, 2 decompensated with recovery, while of the 3 who had chorea 2 decompensated and died. It is interesting to note that these active manifestations of the disease occurred among the patients whose ages ranged from eight-

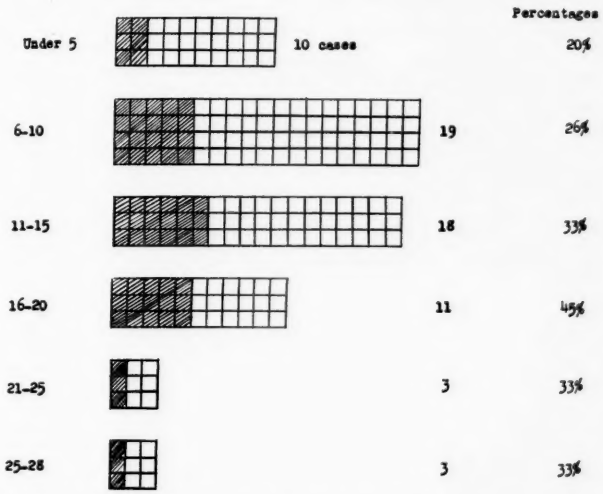

Fig. 4.—Relationship of duration of disease to decompensation. Sixty-six cases of rheumatic heart disease. History of onset of disease obtained. Note: One patient had chorea, first attack with pregnancy, and died. One patient with long-standing mitral lesion had rheumatic fever. Pregnancy and decompensation not included in above analysis.

een to twenty-two years of age, with one exception, a woman of thirty-five. It is important when examining these younger mothers to be alert for the signs of activity of rheumatic process. As decompensation occurs in over 50 per cent, it should be considered a serious complication of pregnancy (Table IX).

4. *Auricular Fibrillation.*—Auricular fibrillation occurred in 7.8 per cent of the rheumatic patients in this series. The ages of the patients who presented this arrhythmia varied from twenty-three to thirty-nine years with one exception, a girl of nineteen who also had signs of active rheumatism. The duration of the heart disease from onset of rheumatic fever to onset of auricular fibrillation varied from eleven to twenty-three years (Table X). The reason that auricular fibrillation

TABLE X. AURICULAR FIBRILLATION

	NO. OF PATIENTS	DECOMP. NO. OF CASES		DEATHS NO. OF CASES	
		DURING PREG.	AFTER PREG.	DURING PREG.	AFTER PREG.
Rheum.	8	6	2	0	3
Arterio.	1	1	0	1	0
Time of decomp.		1 at 3 mo. 2 at 7 mo. 3 at 8 mo. 1—2 days P.P.	1—1 year P.P. 1—5 years P.P.		
Time of death				During labor	1—5 mo. PP. 1—1 yr. P.P. 1—5 yr. P.P.

Age of patients varied from twenty-three to thirty-nine years with one age nineteen.
Duration of disease from onset of rheumatic fever to onset of auricular fibrillation eleven to twenty-three years.
Percentage of rheumatic cases with auricular fibrillation 7.8 per cent.

is not encountered more often in pregnancy may be because women in the childbearing ages are not as a rule old enough for the development of this irregularity. De Graff and Lingg[11] have shown that auricular fibrillation is usually a late manifestation in rheumatic heart disease as it was most commonly observed in the relatively long-standing cases. Auricular fibrillation is usually associated with heart failure. Of 8 cases in rheumatic women, 6 decompensated. The patients with auricular fibrillation with arteriosclerotic heart disease decompensated and died.

DISCUSSION

The problem of heart disease in pregnancy in this locality concerns itself nearly entirely with rheumatic heart disease. In this series 91.8 per cent of heart disease in pregnancy is rheumatic. The number of cases of heart disease due to other etiologic factors is too small to warrant any conclusions.

In this clinic when patients are first examined and the diagnosis of heart disease is completed, a decision is made as to whether, from a consideration of their history, physical findings and functional classification, they will be able to undergo the strain of pregnancy and childbirth. There were 10 women in the series who were judged unable to continue with their pregnancies. These pregnancies were interrupted for one or another of the following reasons: (1) A history of a previous cardiac decompensation. (2) The presence of auricular fibrillation. (3) Functional classification "2B." Class 1 and 2A patients were previously allowed to continue with pregnancy. As 11 per cent of Class 1 and 10 per cent of Class 2A patients decompensated during pregnancy, and two of Class 1 patients died, we realized that the criteria were not sufficient to safeguard the lives of these women and additional factors should be considered.

In addition to the criteria mentioned, the most important factor that should be considered is the extent of the structural damage in the heart.

This may be estimated by the size of the heart and the presence of a long diastolic murmur at the apex.

When the heart size is more than 55 per cent of the diameter of the chest, decompensation occurs in 50 per cent. When the heart size is in excess of 60 per cent, 78 per cent fail and when over 65 per cent all decompensated.

The finding of a long rumbling diastolic murmur at the apex is an ominous sign. It is associated with a high degree of stenosis of the mitral valve and when present decompensation occurs in 62 per cent. This sign was also elicited in 9 of the 13 women who have died since this series was started in 1926.

All of the twelve Class 1 and 2A patients that decompensated with one exception presented either one of these signs, namely, a heart size in excess of 55 per cent of the diameter of the chest or a long rumbling diastolic murmur at the apex. If the importance of these signs had been recognized at the time and the pregnancies interrupted, the decompensations might have been prevented. These signs are indications of advanced heart disease and women with these findings are very poor subjects for pregnancy, and careful contracepsis or sterilization should be seriously considered. This is of importance in clinic patients where there is great difficulty encountered in controlling them. Women will re-enter the clinic at the sixth or seventh month of gestation, pregnant again when every precaution has been advised for its prevention. If the indication exists for interruption of pregnancy, the indication exists for sterilization except perhaps in women with active manifestations of rheumatic disease.

It has been shown that over 50 per cent of the patients in this series that had active rheumatic infection failed during pregnancy. Although the number of instances of this complication was small, the indications from these findings suggest that it is dangerous and calls for prompt interruption of pregnancy. As these women are usually young and the changes in the heart may not be extensive, it is inadvisable to sterilize them, for they may be able to carry through a subsequent pregnancy.

The duration of the rheumatic disease is an important factor in prognosis. If the disease has been present for over fifteen years, the likelihood of extensive changes in the heart is great and decompensation will probably occur in about 45 per cent of the patients. However, it is not recommended that the duration of the disease itself be an indication for interruption unless there are other signs of extensive heart disease.

Auricular fibrillation is generally accepted as an indication for the interruption of pregnancy. In this series, decompensation occurred in 75 per cent. Therefore, in addition to a history of previous decompensation, auricular fibrillation and functional classification "2B" the following indications for the interruption of pregnancy should be added: A

heart size of more than 55 per cent of the diameter of the chest, a long rumbling diastolic murmur at the apex, signs of active rheumatic infection and rheumatic heart disease of more than fifteen years' duration.

FOLLOW-UP

Seventy-eight women have been followed for a period extending from one month to nine years after delivery, 64 of these have been observed for over a year. Of these 78 women 6 died. One died suddenly following a recurrence of rheumatic carditis nine months following pregnancy. Another died five months after an interruption and sterilization. Death was due to cardiac decompensation. Another died two years and six months after last pregnancy with congestive heart failure. The fourth death occurred in a woman who had lived as a chronic invalid in this and the Montifiore Hospitals for four years and six months following her pregnancy. The fifth died four years and seven months after her confinement with a recurrence of rheumatic carditis and cardiac failure. The sixth died from lobar pneumonia six years and five months following her gestation. There are two patients still living who have developed auricular fibrillation since pregnancy and one who when last seen over three years after her last pregnancy was in acute decompensation. We do not believe that any conclusions can be drawn from the follow-up of our 78 patients as to whether they were worse following pregnancy. We are dealing with too many variables other than pregnancy that might influence the patients' condition. The natural progression of the rheumatic lesion alone would influence our conclusions in those that have been followed for a considerable period of time. In order to make any judgment as to the effect of pregnancy on the course of rheumatic heart disease a large number of patients must be followed from infection to death. The duration of the life and morbidity can be compared with a similar series of women who have never been pregnant. Only then will we be able to know definitely whether childbearing shortens the life span in women with rheumatic disease of the heart.

CONCLUSIONS

The use of the functional classification for cardiacs as the only guide, as to whether women undergoing pregnancy will be able to withstand the strain of gestation and labor, is not adequate. It has been demonstrated that other factors have to be considered, namely, the size of the heart, the presence of a long rumbling diastolic murmur at the apex in mitral stenosis, the presence of signs of rheumatic activity, the presence of auricular fibrillation and the duration of rheumatic heart disease.

Only if each case is individualized and all these factors considered can an accurate estimation of the risk entailed be obtained.

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DISCUSSION

DR. T. R. TURINO.—It is a generally accepted fact, that, with few exceptions, in medical or surgical complications of pregnancy our attention should be directed to the treatment of these conditions rather than the pregnancy. This axiom cannot be overemphasized in the management of the pregnant woman with heart disease. It is a problem which should be shared equally by the internist and the obstetrician. In the last five years at the Brooklyn Hospital, we have attempted to fulfill this requirement for care of the pregnant cardiac patient, in that the personnel of the prenatal cardiac clinic is made up of both cardiologists and obstetricians.

In a study of the obstetric aspect of heart disease in pregnancy made upon this group of patients, the following conclusions were drawn.

1. The average length of labor in the cardiac patient was not appreciably different from that in the noncardiac.

2. The incidence of operative interference was high, in order to shorten the second stage of labor.

3. Open drop ether was the anesthetic of choice for delivery.

4. The average weight of the babies born to cardiac mothers was slightly above the average normal.

5. The incidence of spontaneous premature labors was slightly higher.

6. There were 23.6 per cent of the patients in this series who decompensated either in pregnancy or during labor.

7. The uncorrected fetal mortality was 10.4 per cent.

8. Eight mothers died, an uncorrected incidence of 7 per cent. Five of these patients had no prenatal care.

9. The pregnant cardiac patient is best managed through pregnancy and labor by the joint efforts of the internist and obstetrician.

SURGICAL COMPLICATIONS OF PREGNANCY*

S. A. COSGROVE, M.D., F.A.C.S., JERSEY CITY, N. J.
(From the Margaret Hague Maternity Hospital)

NO ONE realizes more thoroughly than the trained obstetrician the profound changes in the maternal organism entailed by pregnancy. He is also thoroughly alive to the interaction between pregnancy and any intercurrent medical or surgical condition from which the mother may suffer. He knows that the prognosis of the pregnancy may be profoundly influenced by the intercurrent condition, and that the course and progress of the intercurrent disease may be very seriously affected by the strain of pregnancy.

But he recognizes also two other considerations: First, the tremendous capacity of the maternal organism for accommodating itself even to double strains of a serious nature; second, that the natural course and termination of the pregnancy in general terms represents less strain and less chance of disaster than does artificial interference with that course and termination.

*Read (by invitation) before the Obstetrical Society of Philadelphia, January 7, 1937.

As my mind goes back over an experience of thirty years, three significant changes in general attitude appear to me to signalize the increasing recognition of these facts. The first obstetric case which I ever "booked" in private practice was a young Irish woman in her first pregnancy, who complained, in her first or second interview, of an acute toothache. I advised her to see her dentist, and, if he thought necessary, to have the tooth extracted. The following day I was summarily dismissed from the case, because she and her mother never heard of any doctor advising a pregnant woman to have a tooth taken out.

Now, note that this family's reaction did not merely represent in that day a matter of lay ignorance, but was representative of an attitude shared alike by the medical and dental professions toward pregnancy. While it is true that the leading teachers in the obstetric field recognized the importance of dental infection and the necessity for its treatment in relation to pregnancy, the rank and file of both professions were reluctant to advise or undertake it.

Today in the Margaret Hague Maternity Hospital, the dental clinic sees about 4,500 cases a year, among which nearly half are referred to the exodontia clinic for extractions.

Our records show only one case of unfortunate outcome of this extensive practice.

E. C. (No. 27,198), a white, twenty-three-year-old primigravida, was admitted to the prenatal clinic, July 13, 1936. Sept. 17, 1936, she had the upper third left molar extracted in our clinic. She subsequently had several other acutely ulcerated teeth extracted by an outside practitioner. Three weeks later, Oct. 7, 1936, she was admitted to the Surgical Service of the Jersey City Medical Center with extensive purulent osteomylitis of the mandible and cellulitis of the cheek and submaxillary area of streptococcic origin. Three drainage operations took place within the next month, the first under evipal anesthesia, the last two under gas oxygen. The day following the last operation she was transferred to us in labor nearly at term and delivered a healthy child under light ether. Four days later she developed extensive bronchopneumonia, subsequently empyema, and died on the fifteenth postpartum day.

This woman was pregnant; she had a tooth extracted; she died! But this sad history is not different from the occasional case seen in the nonpregnant; there was no deleterious effect on her pregnancy, due to the dental operations; and there is no likelihood that the occurrence of labor during her protracted septic illness predisposed to the fatal outcome, save in one lapse of art. The administration of inhalation anesthesia twice in twenty-four hours, once by the surgeons, and once by ourselves in the presence of a foul infection of the mouth, perhaps places responsibility for her death squarely on that mismanagement.

As long ago as the time of Paré, that omniscient genius who prophesied that there would probably be but little significant advancement in the knowledge and practice of surgery beyond that to which he had

himself attained, down to the time that McPheeters wrote his very significant monograph in 1929, there had been an almost universal consensus that varicose veins in pregnancy were not susceptible to any except expectant treatment. In our own prenatal clinic we have so far given 3,445 injections for varicosities to 695 patients. Most of these have been in the lower extremities, but we have not hesitated to inject varicosities of the vulva and of the vagina. To the best of my knowledge, hospitalization for complications following this type of treatment has been necessary in only one case where a rather extensive slough developed over the site of injection, and one case of extensive severe cellulitis of the thigh and leg.

The textbook I used as a student was the then new, elaborate and very modern first edition of J. Clifton Edgar's *The Practice of Obstetrics.*

Dr. Edgar says of the "Curative treatment" of eclampsia, i.e., after the onset of convulsions, "empty the uterus under deep anesthesia by some method that is rapid and that will cause as little injury to the patient as possible." "Many cases that could ... be saved will probably succumb if ... the teachings are followed ... that the eclamptic uterus should not be disturbed ...." " ... There is scarcely an authority of the present day who absolutely rejects local interference ...." " ... The best authorities are in favor of emptying the uterus as quickly as possible." "Expectant ... treatment will almost surely be followed by the death of the child and about one-third of the mothers ...." "But if the uterus is promptly evacuated by suitable surgical means ... the mother is practically subjected to no danger." "The popular method of the present day seems to be mechanical dilatation of the cervix and prompt extraction of the fetus. This method is safe and effective when properly performed." Yet he states that it will often take an hour and a half (under *deep* anesthesia!) and dilates on its many difficulties and dangers.

The almost complete unanimity of opinion at the present time in substituting entirely expectant treatment of the eclamptic mother for this universal interference so insisted upon by the leading authorities of scarcely more than a quarter of a century ago, represents perhaps the most significant improvement of obstetric practice during that period.

Similar conservative tendencies in the last few years have seemed to be more or less realized in relation to other complications, such as cardiac diseases and tuberculosis. I am inclined to think that the feverish furore to utilize so-called therapeutic abortion in the presence of hypertensive and nephritic toxemias, now noticeably rampant in some clinics, will presently give way to a saner and more balanced management of these cases.

The change in ideas of management of the three frequent and important complications of pregnancy, which I have alluded to, has seemed to me to exemplify a change of thought toward all complications of pregnancy.

The end-result of such general change might then be expressed as follows: The other diseases which may occur concomitantly with preg-

nancy should, in general, be thought of, and managed, just as though the pregnancy did *not* exist, and the pregnancy itself should *not* be interfered with because of the simultaneous occurrence of such diseases.

I had supposed that this statement did actually represent almost universal opinion and practice, until one of my students challenged me by saying that one of his teachers did not think as I did in relation to appendicitis. Thus challenged, I reviewed the expression of several recent writers relative to this particular condition.

The opinions of authors of recent obstetric texts are quite unanimously in line with noninterference, although DeLee implies the occasional advisability of Porro section in relation to appendicitis in late pregnancy.

To quote rather fully from the 1933 edition of DeLee, he says that the greater seriousness of the results and prognosis of appendicitis, particularly in late pregnancy, depends on:

1. The fact that protective adhesions do not form so well because of dislocation of relation of the appendix, the gut and the omentum by the uterus.

2. Inflammatory processes tend to be more acute because of increased general vascularity of the pelvic abdomen.

3. Because of the same factor, thrombosis and phlebitis tend to occur more frequently.

4. Because of the upward dislocation of the appendix, suppuration, when it occurs, involves the higher and less resistant portions of the peritoneum.

5. Because of the occupancy of the greater part of the abdominal cavity by the uterus, drainage of pus is less facile and it tends to burrow more extensively.

6. Because of the distention of the abdomen by the uterus the occurrence of intestinal distention in connection with the appendicitis itself, and operative procedure undertaken in its treatment causes more embarrassment of respiration, and more frequent pulmonary complications.

7. For the same reason intestinal obstructive symptoms are more frequent and occur earlier.

8. There is considerable risk of bacterial infection of the placental site.

Many other authors recognize the validity of these modifying factors represented by pregnancy.

DeLee further says: "All of these considerations combine to cause a very high mortality after labor occurs as the contractions of the uterus may rupture the appendix itself, or the walls of an abscess cavity, particularly in the third stage and puerperium. The mortality in appendicitis complicating late pregnancy or labor is 40 per cent. In regard to the operative management, however, he says:

"The uterus is manipulated as little as possible, . . . 'Get in and get out quickly' . . . " and states further that cesarean section is contra-indicated.

Beck in his *Obstetrical Practice*, published in 1935, says: "In reference to operative treatment of appendicitis in late pregnancy, handling of the uterus . . . is to be avoided as much as possible . . . , and makes no reference at all to direct operative interference with pregnancy as part of the surgical treatment of the complication.

Schumann, in his *Textbook on Obstetrics*, in 1936, says of the operative treatment of appendicitis, that hysterotomy should never be attempted.

Stander, in the 1936 edition of *Williams Obstetrics*, mentions the suggestion of some authorities to perform cesarean section at the same time as operating for appendicitis, but expresses his firm conviction that this procedure will generally increase the gravity of the situation.

When wider reference to published opinion is made, however, the conservative expressions of the authors quoted is not found to be unanimously endorsed with reference to those cases occurring late in pregnancy, or in labor.

Among those who concur with conservative practice are Norton and Connell, of our staff, who recently reviewed eight cases from our own service, and who conclude: "Acute appendicitis with peritonitis complicating labor, should be managed surgically as it is at any other time, and the labor allowed to continue with delivery through the birth canal, in the absence of an indication requiring a different obstetrical procedure."

Maes stresses the importance of prompt surgical intervention in appendicitis complicating pregnancy, but says "... the gravid uterus should be handled as little as possible," and emphatically denounces as pernicious and unwarranted any operative interference with the pregnancy at the same time.

McDonald says that "... an acute abdomen with probable peritonitis is an unfavorable field for hysterotomy," and that radical termination of pregnancy will not at all relieve the load of sepsis and impending labor; that "hysterotomy ... is a desperate procedure for a condition already nearly hopeless.... Abdominal section is... only too popular. ... For the condition under consideration it has a number of overwhelming contra-indications," among which are:

1. There is great danger of directly infecting the uterus.
2. The uterus may not heal well, and may rupture in subsequent pregnancies.
3. It is obstetrically objectionable in young women with no permanent dystocia.

He concludes, "I can find no justification for abdominal hysterotomy unless labor is imminent, *and there is actual dystocia* which prevents vaginal delivery."

Robert A. Kimbrough of Philadelphia in a personal communication states that he is quite in accord with a wholly conservative attitude.

Krauss, Barber and Miller, Portes and Sequy, among others support this view.

Many authors take a somewhat modified stand, which is fairly representatively expressed by Heineck, who says that it may be necessary to resort to vaginal or abdominal cesarean section where coexistence of obstetric complications such as definite pelvic contracture or placenta previa requires unusual methods.

But there is a not inconsiderable number of writers who are so obsessed with the danger of labor activity on the course and outcome of concurrent appendicitis, that in late pregnancy they do not hesitate to advise termination by:

1. Vaginal delivery before opening the abdomen to treat the appendicitis, even to the extent of employing forcible dilatation of the cervix, or vaginal cesarean section.
2. Abdominal hysterotomy at the same time that the appendix is dealt with.
3. Removal of the uterus at the same time as appendicectomy is done.

Thus Maes quotes Cooke and Mason "complacently mentioning" accouchement forcé in multiparas in expert obstetric hands.

He also quotes DeLee as believing low cervical section safe if the patient is in labor, but we have already seen that DeLee in later writings does not advise this procedure.

Marbury says: ". . . it may be wiser to make a paramedian incision and empty the uterus by cesarean section first, and deal with the appendix secondarily. This

permits the operator to determine the degree of soiling after the uterus has contracted, and make a more definite and permanent toilet of the abdomen.''

Paul Titus quotes, and apparently concurs with Marbury in favor of hysterotomy, and, in the presence of peritonitis, hysterectomy.

B. C. Hirst has been repeatedly quoted as in favor of hysterotomy in the presence of generalized peritonitis.

Wilson says with reference to appendiceal abscess in late pregnancy, ''... labor will follow operation within a few days with disastrous results.... the uterus should be emptied at the time of operation in the interest of both mother and child.'' ''If a marked peritonitis is present... a rapid Porro operation is the safest procedure ....'' ''The two-flap, low section... ranks next to the Porro operation for safety, whenever it can be properly performed. The classical section, because of its simplicity, is the method best adapted for most cases and... will yield good results. ... In the last dimester... cesarean section, followed by appendicectomy, is advocated as the procedure which will give the best results.''

King suggests emptying the uterus before performing appendicectomy, to reduce its size and facilitate the latter operation.

Rose says the consensus is, that in the presence of rupture and localized or spreading pus infection late in pregnancy, it is best to remove the appendix and do a Porro section.

Schmid, Puppel, La Jemtel are among others who concur in this alleged consensus.

This brief review of opinion shows that in early pregnancy there is complete agreement as to the wisdom of noninterference with pregnancy in the presence of acute appendicitis and its sequelae. But where the latter condition complicates the last two months of gestation, and especially when labor is imminent or actually in progress, there is sharp divergence of practice.

It seems to me that acute appendicitis is a sufficiently frequent and certainly serious enough complication of late pregnancy to have our practice standardized.

I would therefore invite your attention to the following cases of surgical complications of pregnancy occurring in our own clinic. It will be observed that they do not include:

a. Cases in which the surgical indication is purely obstetric, as ectopic gestation, rupture of the uterus, mechanical dystocia, abruptio placentae.

b. Cases which by their nature necessarily involve sacrifice of the gestation, as fibroids incompatible with continued evolution of pregnancy, or carcinomata uteri.

c. Cases where, in a dying mother, antemortem section is done wholly in the interest of a living fetus.

COMMENT

These cases fall into three groups: First, cases of appendicitis in the first seven months of gestation, in which all the mothers survived, as did all but three[3] of the babies, the causes of these deaths being severally discussed. As previously indicated, this group does not fall into

TABLE I

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY M	MORTALITY B
1. V.D. 12726 4/18/33	Normal pregnancy Ac. gangrenous appendicitis, 6th mo. appendicectomy, drainage	Normal parturition. Term	L	L
2. F.S. 13229 4/21/33	Nephritic toxemia, pregnancy Missed abortion, 4th mo. Ac. gangrenous appendicitis, 7th mo. Appendicectomy	Spontaneous extrusion conception product 3rd p.o. day	L	D
	No p.o. morbidity; death of baby not related to appendicitis; abortion did not disturb course.			
3. A.K. 13604 5/9/34	Normal pregnancy Ac. gangrenous appendicitis, 5th mo. Appendicectomy	Parturition normal Term	L	L
4. E.H. 16179 2/18/34	Normal pregnancy Ac. purulent appendicitis, 6th mo. Appendicectomy	Normal parturition Term	L	L
5. H.O'B. 17672 4/31/34	Normal pregnancy Ac. ulcerative appendicitis, 5th mo. Appendicectomy	Normal parturition Term	L	L
6. R.G. 18904 8/12/34	Normal pregnancy Ac. gangrenous appendicitis, 2nd mo. Appendicectomy	Normal parturition Term	L	L
7. M.B. 22430 5/17/35	Normal pregnancy Ac. ulcerative appendicitis, subac. bilateral salpingitis, 3rd mo. Appendicectomy Salpingectomy	Normal parturition Term	L	L
8. H.E. 993 11/23/35	Abnormal pregnancy Cornual implantation, threatened abortion Ac. catarrhal appendicitis, 3rd mo. Appendicectomy	Spontaneous complete abortion 28 days p.o.	L	D
	Death of baby dependent on abnormal implantation; operation did not hasten outcome.			
9. M.N. 25259 12/29/35	Normal pregnancy Recurrent ac. ulcerative appendicitis, 3rd mo. Large lutein cyst left ovary Appendicectomy Oophorectomy	Aborted spontaneously completely, 6th p.o. day	L	D
	Fetal death due ovarian pathology and removal; abortion did not disturb afebrile course.			
10. A.O'C. 25872 2/20/36	Normal pregnancy Ac. catarrhal appendicitis Multilocular intraligamentous cystadenoma of ovary, 3rd mo. Appendicectomy Extirpation of cyst.	Normal parturition Term	L	L

TABLE II

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY M	MORTALITY B
11. J.B. 8404 2/13/33	Normal pregnancy Ac. purulent appendicitis, 8th mo. Appendicectomy	Premature parturition 3rd p.o. day	L	L
	Difficult delivery of appendix from retrocecal bed—Postoperative course was completely afebrile; early parturition *did not* disturb it.			
12. T.D. 8382 4/12/33	Normal pregnancy Ac. purulent appendicitis local peritonitis, 9th mo. Appendicectomy Drainage	Normal parturition Term, 15 p.o. day	L	L
	One day febrile morbidity, except for mammary abscess on 21st p.o., 6th p.p. day; delivery was *not* precipitated by operation; smooth postoperative convalescence was *not* modified by delivery.			
13. M.M. 4867 9/3/34	Normal pregnancy Ac. purulent appendicitis 9th mo. Appendicectomy	Normal parturition Term, 22 days p.o.	L	L
	One day p.o. febrile morbidity; operation did *not* precipitate delivery			
14. J.H. 19680 12/20/34	Normal pregnancy Ruptured gangrenous appendicitis with twisted pedicle cyst of ovary and peritonitis, *intrapartum* Appendicectomy and drainage	Normal parturition (low forceps to expedite) 1 day p.o.	L	L
	This case reported in detail by Norton and Connell; actual labor had begun before operation. Operation did *not* essentially modify course of labor; labor *did not* modify smooth p.o. convalescence.			
15. E.T. 20669 1/3/35	Normal pregnancy Subacute appendicitis, 8th mo. Appendicectomy	Normal parturition Term (low forceps to expedite)	L	L
16. M.D. 23958 8/27/35	Normal pregnancy Ac. perforated appendicitis with general peritonitis, 8th mo. Appendicectomy, drainage Secondary drainage Laparotomy; enterostomy	Spontaneous premature delivery, 10 days p.o.	D	L
	Patient admitted 2 days after onset, with repeated purgation during that interval, and with extensive generalized peritonitis. Immediate prognosis was most grave, and course so unsatisfactory that secondary drainage operation was performed *before* labor had occurred, and could be assessed as a factor of disturbance. Fatal outcome believed to depend on delayed diagnosis and early mismanagement, and to be expected even had patient not been pregnant. Further believed that augmentation of original operative shock by *any* method of emptying uterus at that time would have been fatal.			

TABLE II—CONT'D

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY M	MORTALITY B
17. H.K. 26461 8/20/38	Normal pregnancy, term Ac. purulent appendicitis Appendicectomy, drainage	Normal parturition 24 hours p.o.	L	L
	Local purulent peritonitis present; appendix was exposed with much difficulty; only 2 days p.o. febrile morbidity. Labor did *not* modify the good postoperative course.			
18. H.M. 28154 10/27/36	Normal pregnancy, term in labor Ac. purulent appendicitis intrapartum Appendicectomy, intrapartum	Normal parturition 24 hours p.o.	L	L
	Active labor commenced at least two hours before operation, and perhaps earlier, as it was hard to distinguish labor contraction in the presence of the severe inflammatory pain, so that operation did not initiate labor, nor modify its normal evolution. Neither did labor modify a smooth postoperative course, marked by only 2 days' febrile morbidity.			

the field of controversy, as all commentators agree that no disturbance of pregnancy is necessary thus early in pregnancy.

Second: cases of acute appendicitis occurring in the eighth and ninth months of pregnancy, two of them intrapartum. One mother died, but all the babies survived. There is some detailed discussion of each of these cases.

Eight of the cases in these two groups have been previously reported by Norton and Connell.

Third: a small group of miscellaneous intraabdominal surgical complications, each of which is discussed. One mother and two babies died.

In reviewing the case discussions, our experience would not appear to lend much support to several of the factors of fear in relation to appendicitis in late pregnancy included in the opinion of DeLee and others already quoted. Certain of them appear theoretical rather than based on factual observations. Thus, in our several cases of ruptured appendix with peritonitis, drainage appeared to be just as effective, and postoperative course just as smooth, as it could reasonably be expected to be in the nonpregnant. Our mortality, even in the severe cases late in pregnancy, does not approach the high percentage quoted by DeLee.

The theoretic risk of infection of the undisturbed placental site is not, in our opinion, nearly so real as the actual risk of infecting the site should the uterus be opened transperitoneally, nor of infecting the broad lymphatic and cellular tissue areas exposed in extirpating the uterus.

The fear of tearing the appendix or adhesions would appear to overlook the extreme mobility of all the abdominal viscera, and the possibility thereby of mutual accommodation to shifting relationship in spite of extensive inflammatory adhesions.

This accommodation is so usual a part of the natural history of all intraabdominal inflammatory states in relation to the natural functioning of all the viscera, that undue alarm concerning the equally natural functioning of the uterus is hardly warranted.

So also the fear that "labor will follow operation within a few days with disastrous results" is not substantiated in our experience, as several of our cases have delivered in from a few hours to several days without such disaster.

On the other hand, it does not seem to us tenable that the emptying of the uterus by any of the proposed interfering procedures can in any possible way be "in the interest of" the mother. The opening of the highly vulnerable genital tract to the direct invasion from contiguous

TABLE III

IDENTITY ADM. DATE	DIAGNOSIS AND OPERATION	OUTCOME OF PREGNANCY	MORTALITY M	MORTALITY B
19. M.F. 16823 1/29/34	Normal pregnancy Twisted pedicle ovarian cyst 3rd mo. Oophorectomy	Normal parturition Term	L	L
20. G.R. 12472 6/23/34	Normal pregnancy Twisted pedicle lutein cyst of ovary, 3rd mo. Oophorectomy	Incomplete abortion 11 days p.o. Digital extraction secundines	L	D
	Fetal death probably due to nature of pathology			
21. E.S. 21686	Normal pregnancy Pedunculated fibroid Ac. hemorrhagic degeneration, 4th mo. Resection of tumor involving myometrium of fundus	Parturition normal Term	L	L
	As is not infrequently observed, even incision into the substance of the pregnant uterus itself may not disturb the pregnancy, nor result in dangerous weakening of the wall thereof.			
22. A.G. 24139 9/16/35	Normal pregnancy Ac. hemorrhagic pancreatitis; general peritonitis, 7th mo. Exploratory laparotomy, drainage.	Spontaneous premature delivery (elective low forceps to expedite) 15 hours p.o.	D	D
	Patient admitted 2 days after onset of acute symptoms, with background of acute alcoholism and severe abdominal trauma—symptom picture was confusing. The acute surgical condition with its severe toxicity doubtless caused fetal death and precipitated delivery. The upper abdominal exploration can hardly be held to have done so. The parturition almost certainly did not malignly affect the already hopeless condition of the patient.			
23. H.B. 20673 12/6/34	Normal pregnancy Adenocarcinoma of ovary, 6th mo. Salpingo-oophorectomy	Spontaneous premature delivery, 32 weeks, 33rd p.o. day	L	L
	Subsequent to operation there was a series of intensive deep x-ray exposure. This may have induced premature labor. The operative interference per se could scarcely have done so, as more than a month had elapsed following it. At present, 2 years later, mother and babe are in apparent good health.			

dangerously inflamed tissue is alike poor obstetrics and poor surgery. Hardly less defensible is the breaking down of natural peritoneal barriers by the extensive dissection involved in hysterectomy.

It may here be objected that only one of our cases actually had a full-blown general peritonitis; that she died; and that it is particularly in this type of case that radical measures are advised. Others of our cases, however, have been ruptured and have had at least beginning peritonitis, thereby falling into the group of most serious potentiality. And in this connection I believe it generally sound, that the sicker the patient, the more essential it is to limit surgery to the absolute minimum consistent with extirpation of the focus of trouble and adequate provision of drainage. Beyond that, the natural resistance of the patient and the uninterfered-with maintenance of all her normal functions offer the best prognosis.

Based then on the 23 cases of acute abdominal surgical necessity occurring in 25,000 living births, I would state as justifiable conclusions:

1. Acute appendicitis is a surgical condition invariably calling for prompt operative intervention.

2. This indication is not modified, but is even more promptly imperative when appendicitis complicates pregnancy, even at or near its termination.

3. Its surgical treatment should *not* be combined with any manipulation to terminate pregnancy. This statement may be modified only by:

a. The legitimacy of simple procedure to expedite termination of the second stage of spontaneous labor;

b. Recognition of the very rare possibility of concurrent serious factors of obstetric dystocia. When this occurs, recourse may be necessary to delivery by the abdominal route. But such interference should be reserved until after the onset of spontaneous labor, and an extraperitoneal approach selected.

4. The same principle applies in other surgical complications of pregnancy.

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THE MORTALITY AND COMPLICATIONS OF 3,129 SUPRACERVICAL HYSTEROMYOMECTOMIES*

HERBERT E. SCHMITZ, B.S., M.D., F.A.C.S., CHICAGO, ILL.

A DISCUSSION of the advantages and disadvantages of total versus subtotal hysterectomy has usually resulted in the expression of a divergence of opinion. Such reports were usually based on the good end-results of patients treated by the reporting surgeon in his service at the hospital. Depending on skill and experience the reports depicted the surgeon's mastery of either one of the techniques but did not settle the question of the fate of the patient after the operation, if subjected to a total or subtotal hysterectomy. This study was prompted by the belief that a complete analysis of a large series of cases, performed by a group of gynecologists in a charity hospital, would give more definite data. The cases here presented comprise all the supravaginal hysterectomies performed at the Cook County Hospital for myomas of the uterus during a ten-year period and listed as such in the hospital record room. The study comprises a review of the records during the ten years from 1926 to 1936.

Dixon[1] considers myoma the most frequent tumor in the human body and quotes Bland as saying that 20 per cent of all women have fibromyomas after the age of thirty-five. Davis and Cusick,[2] in a critical study of 335 hysterectomies, conclude that hysterectomy is the operation of choice for fibromyomas of the uterus. It was done in approximately 72 per cent of their series. The same percentage of hysterectomies for myomas also prevailed in the clinics of 45 of our leading operators in this country and Canada.

This report considers the type of patients, the associated pathology, the postoperative complications, and the mortality of supravaginal hysterectomies performed at the Cook County Hospital during the past ten years.

TYPES OF PATIENTS

County charity hospitals accepting all patients that apply for treatment receive many far-advanced and neglected cases. Operations oftentimes are deferred for days in an attempt to build up the patient's general condition by bed rest, proper food, care of the bowels, removal of foci of infection, and in severe secondary anemias by transfusion of whole blood.

About half of all the patients on the gynecologic service are negroes, and many of them, as well as a fair number of white women, have a four-plus Kahn or Wassermann reaction. There is a high incidence of pelvic infection among these patients, thus adding to the operative

*Read before the Chicago Gynecological Society, January 15, 1937.

risk. The seven regular attending gynecologists performed most of the operations but a few were done by the general surgeons, by associates and by senior internes under the direct supervision of the senior attending gynecologists.

ASSOCIATED PATHOLOGY

Of the 3,129 cases reviewed, 1,323 or 42 per cent had associated pathology complicating the myoma. Chronic salpingitis was by far the most frequent complication, being present in 834 cases or 26 per cent. Other types of inflammatory conditions were present in 1,185 or 38 per cent of the cases. Tubo-ovarian abscess, pyosalpinx, pelvic abscess, and chronic pelvic peritonitis composed the other 351 infections. Table I shows the complete list of all the associated pathologic conditions listed in the order of their frequency. Both the operative and pathologic reports were studied for this information.

TABLE I. ASSOCIATED PATHOLOGY IN ALL CASES

Chronic salpingitis	834	Pelvic endometriosis	1
Hydrosalpinx	118	Chondroma	1
Tubo-ovarian abscess	100	Sarcoma	1
Pyosalpinx	65	Anaplastic squamous cell carcinoma of ovary	1
Chronic pelvic peritonitis	61	Brenner tumor	1
Degenerated myoma	35	Gärtner's duct cyst	1
Intraligamentous myoma	20	Bicornate uterus	1
Dermoid cysts of the ovary	20	Gangrenous appendix	1
Uterine pregnancy	11	Retained stem pessary	1
Hematosalpinx	8	Missed abortion	1
Pelvic abscess	7	Papillary cyst adenocarcinoma of ovary	1
Large simple cysts of ovary	6	Carcinoma of fundus	1
Tubal pregnancy	5	Accidental tear of bladder	1
Placental remnants	3	Accidental perforation of rectum	1
Placental polyp	3	Thrombophlebitis	1
Carcinoma of the cervix	2		

Simple cysts of the ovaries, slight fibrinous adhesions and unusually large myomas were not included as complications. They occurred in numerous instances but added nothing to the surgical procedure. Ovarian cysts were included only when larger than a fetal head. Intraligamentous myomas were listed only when the layers of the broad ligament had to be separated to expose them. Small nodes pushing out into the broad ligaments were not considered. Patients reported as having pelvic peritonitis are those having dense adhesions of bowel, omentum, and oftentimes bladder. Minor adhesions of adnexa and rectosigmoid because of a gonorrheal salpingitis and pelvic peritonitis were reported as salpingitis or diseased adnexa. The tubal pregnancies, one of which had ruptured, were all undiagnosed but the uterine pregnancies complicated by myomas were diagnosed in four instances and unrecognized in seven.

The incidence of malignancy complicating the myomatous uterus or cervix is not considered here because of the fact that the cases diag-

nosed during operation are filed in the hospital records as malignancies and not under the group of myomas. The four cases were unrecognized grossly and filed under myomas before the pathologic diagnosis was returned.

POSTOPERATIVE COMPLICATIONS

There were 182 or 5.8 per cent postoperative complications. The criteria for morbidity were the necessity for remaining in the hospital more than four days beyond the average stay of ten days or a temperature over 101°. The high incidence of pelvic infections present in these cases at the time of operation is most likely the responsible factor in the production of wound infection.

TABLE II. POSTOPERATIVE COMPLICATIONS

Wound sepsis	126	Fecal fistula	1
Postoperative pneumonia	9	Parametritis	1
Localized peritonitis	8	Psychosis	1
Pelvic cellulitis and abscess	8	Acute pharyngitis	1
Vaginal hemorrhage	7	Central nervous system syphilis	1
Secondary wound suture	4	Accidental tear of bladder	1
Thrombophlebitis	3	Erysipelas of back	1
Cystitis	3	Auricular fibrillation	1
Evisceration	2	Diabetes mellitus	1
Hematoma of wound	1	Vesicovaginal fistula	1
Bleeding from wound	1		

Burch and Burch[3] in reporting a series of 200 hysterectomies performed at Vanderbilt University Hospital, list the complications of the fibromyoma cases and those of pelvic inflammations. The incidence of wound infection in the fibroid group was 9.1 per cent while in the latter group it was 23.2 per cent. Table II lists all the postoperative complications.

Table III gives the morbidity in 1,159 cases of supravaginal hysterectomy performed for myomas and reported by Read and Bell.[4]

TABLE III. MORBIDITY TABLE OF READ AND BELL

Unknown	138	7.9%	Secondary hemorrhage	5
Wound sepsis	52	3.0%	Malignant cachexia	5
Pulmonary complications	35	2.0%	Tonsillitis	4
Femoral thrombosis	35	2.0%	General peritonitis	2
Urinary infection	28	1.6%	Acute dilatation of stomach	2
Septic case	17	1.0%	Parotitis	2
Ruptured abd. wound	12	0.7%	Broad ligament hematoma	2
Wound hematoma	9	0.5%	Auricular fibrillation	1
Parametritis	5	0.3%	Septicemia	1
Intestinal Obstruction	1			

The morbidity in this series amounts to 20.6 per cent; however, the authors mention that of the 138 unknown cases many were detained in the hospital because of improper home facilities or other unimportant causes.

MORTALITY

There were 78 deaths, a mortality rate of 2.1 per cent. This is exactly the same death rate as reported by Read and Bell for 1,739 supravaginal operations performed by the staff of the Chelsea Hospital during a ten-year period.

Table IV lists the causes of death in the order of their frequency. In only a few instances were autopsy reports attached to the history. In the remaining cases the cause of death was taken from the follow-up record and checked by the recorded findings. Greenhill[5] in a study of the deaths following 6,022 gynecologic operations performed at the Cook County Hospital divides the mortality of supravaginal hysterectomy into two groups. In uncomplicated supravaginal hysterectomies it was 0.8 per cent. In supravaginal hysterectomies plus bilateral salpingo-oophorectomy it was 8.9 per cent. The total number of deaths in the fibroid group of his series was 69, of which 51 followed the supravaginal operation. Four occurred after the uterus alone was removed, four after the uterus, both tubes and one ovary were removed and forty-three after the uterus and both tubes and ovaries had been extirpated. In many of the cases in which both adnexa were removed, inflammatory adhesions bound these structures to the uterus and culdesac, adding greatly to the difficulty of performing the operations.

TABLE IV. MORTALITY IN ALL CASES

Generalized peritonitis	36	46.2%	Toxic Goiter	2
Surgical shock	20	25.6%	Injury to bowel and peritonitis	1
Secondary hemorrhage	6	7.7%	Evisceration	1
Pneumonia	4	5.1%	Cardiac failure	1
Embolism	3	3.8%	Meningitis	1
Uremia	2		Ischiorectal abscess	1

The incidence of peritonitis among the deaths in Greenhill's cases was 50.8 per cent, while embolism occurred in 13 per cent. Embolism according to Read and Bell is more likely to follow subtotal hysterectomy for fibroids than for any other operation. It was responsible for 35.1 per cent of the deaths in their series while peritonitis only occurred in 8.1 per cent. In the present series embolism occurred in but 3.8 per cent while peritonitis was responsible for 46.2 per cent. The high incidence of pelvic infection is also responsible for this difference.

The operations performed in the 78 fatal cases are given in Table V.

TABLE V. OPERATIONS FOR THE 78 FATAL CASES

Abdominal supracervical hysterectomy	5
Abdominal supracervical hysterectomy, bilateral salpingo-oophorectomy	71
Abdominal supracervical hysterectomy, bilateral salpingectomy, unilateral oophorectomy	2

This clearly demonstrates the increased risk of removing both adnexa with the uterus. Undoubtedly, if the adnexa had not been so badly diseased and adherent to the structures within the pelvis, the mortality would not have been as high as it was. Therefore, pelvic peritonitis greatly adds to the risk of a supravaginal hysterectomy.

In 68 of the fatal cases the myomas were complicated by pelvic inflammatory disease, an incidence of 85 per cent. The remaining complications were a twisted ovarian cyst with a uterine pregnancy, intraligamentous fibromyoma, Meckel's diverticulum, tubo-ovarian abscess and an accidental bladder injury.

A comparison of the mortality for supracervical hysterectomy in other large series is shown in Table VI. This has been taken from Read and Bell with the addition of the series of Samuels and Edlavitch,[7] Danforth[6] and Greenhill. Table VII also taken from Read and Bell gives the mortality in large series of supracervical hysterectomies performed for fibromyoma of the uterus.

TABLE VI. MORTALITY FOR SUPRACERVICAL HYSTERECTOMIES FOR VARIOUS INDICATIONS

Read and Bell	1739	2.1%
Greenhill	1408	4.6%
Amreich	1253	1.6%
Fullerton and Faulkner	609	4.4%
Danforth	304	0.28%
Samuels and Edlavitch	303	2.6%
W. Fletcher Shaw	232	3.05%
Masson	217	1.8%
Burch and Burch	166	4.2%
Weibel	—	4.25%

TABLE VII. MORTALITY FOR SUPRACERVICAL HYSTERECTOMIES FOR FIBROIDS

Mayo and Mayo	3085	1.2%
Schmitz	3129	2.1%
Read and Bell	1159	2.0%
Alsobrook	1000	2.7%
Amreich	624	1.4%
Lockyer	284	1.76%
Miles Phillips	258	1.16%

SUMMARY AND CONCLUSIONS

1. The mortality of 2.1 per cent in the series of 3,129 cases compares favorably with that of other large series on similar types of patients.

2. Fibromyomas of the uterus are the most common tumors found in women and necessitate about 72 per cent of all supracervical hysterectomies.

3. Inflammatory disease of the pelvis complicated 38 per cent of this series of fibroid cases and greatly adds to the operative risk and mortality.

4. The most frequent causes of death in this series were generalized peritonitis in 46.2 per cent; shock in 25.6 per cent; hemorrhage in 6.7

per cent; pneumonia in 5.1 per cent and embolism in 3.8 per cent. Embolism occurred less frequently than in similar series reported by various authors.

5. Seventy-one of the 78 fatal cases had supracervical hysterectomy plus total salpingo-oophorectomy. As shown by Greenhill in the same group of cases, such operations are the most serious because the mortality for this operation is about ten times as great as for simple uncomplicated supravaginal hysterectomy.

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DISCUSSION

DR. J. P. GREENHILL.—I do not think there is much value in comparing the results obtained at the Cook County Hospital with those at other hospitals because of the difference in the types of patients operated upon. The chief value of such an analysis as Dr. Schmitz has presented is to the surgeons whose cases were analyzed.

As Dr. Schmitz has shown, there is a vast difference in the results of supracervical hysterectomy and this operation combined with removal of both adnexa. I found this to be true in my series of cases where the greater operation had a mortality eleven times as high as the simple supracervical operation. Because of this, I do not hesitate to leave a portion of inflamed tube or ovary attached to adherent bowel rather than forcibly to separate the badly infected adnexa from the intestines. The risk of damage to the intestines is thus eliminated and in my follow-up of many of these patients I have not seen any harm from leaving portions of adnexal tissue attached to the bowel.

In my series, among the patients who had only a supracervical hysterectomy the death rate was 0.8 per cent, whereas among those who had a supracervical hysterectomy combined with removal of both tubes and ovaries, the mortality was 8.9 per cent, or eleven times as great.

DR. FRED L. ADAIR.—Dr. Schmitz gave a total of 78 fatal cases with simple supracervical hysterectomy and 7 with removal of both adnexa. The mortality figures would be more significant if we knew the number of operations done in each of these two groups.

DR. HAROLD O. JONES.—I would like to ask if Dr. Schmitz intentionally omitted endometriosis as a complication in fibroids for it has been common in our experience.

DR. SCHMITZ (closing).—I did not include endometriosis because that condition is not filed as myoma in the record room at the County Hospital, and it would have been too much labor to have gone through ten years of records.

Although I believe the value of this presentation is mostly for those who are doing the work, I have tried to compare the mortality rate with other large series of cases taken from similar charity institutions. As I said, it compares favorably with those.

SPLENOMEGALY IN PREGNANCY*

WILLIAM B. SERBIN, M.D., CHICAGO, ILL.

(From the Obstetrical Services of Michael Reese and Wesley Memorial Hospitals)

ENLARGEMENT of the spleen as a complication in pregnancy and labor is sufficiently rare to warrant the addition of all observed cases to the literature. Within a period of four months three such cases were observed, two occurring in Banti's disease and one in chronic malaria. Splenic tumor has also been reported in purpura hemorrhagica complicating pregnancy.

Allen (1924) reported two cases of splenic anemia complicating pregnancy. The first patient died suddenly during delivery; the second patient was treated with x-rays and carried to term in her first pregnancy. In her second pregnancy therapeutic abortion and sterilization were done and followed in one month by splenectomy. The spleen weighed 885 gm.; there was no liver involvement and the patient recovered. Birdsall, Hubert and Whelchel (1925) reported a case of splenic anemia which they called Banti's disease in its terminal stage, in a primipara, aged thirty-three. During pregnancy there was a progressive anemia treated by transfusion. The patient had a spontaneous delivery at term; the baby was stillborn. The spleen and liver were both enlarged and the patient continued to have uterine bleeding. She improved slowly; there is no mention of splenectomy. Hesseltine (1930) reported a case of Banti's disease in a patient aged forty-two who had had progressive enlargement of the abdomen for two years prior to her pregnancy. In the second trimester a splenectomy was done. The patient went to term and delivered spontaneously. Ashton (1934) reported a case of Banti's disease in the puerperium in a para i aged twenty-five. The patient had had a moderate anemia; she had a ten and three-quarter hours' labor at term; forceps delivery followed by postpartum hemorrhage. On the fourth postpartum day she had a palpable spleen and was given a transfusion. Five months after delivery a splenectomy was done followed by blood transfusion. The liver was small, firm, and hobnailed. The patient died on the thirty-third postoperative day following the removal of packing. Larrabee (1934) gives a brief history of a patient aged twenty-five who aborted five months previous to her admission on a medical service. She had an ascites; splenectomy and transfusion were done. The spleen weighed 420 gm.; there were marked fibrosis and cirrhosis of the liver. Smith, Morrison and Sladden (1933) reported a case in a patient aged thirty-one years, three months pregnant. The patient had a splenomegaly with a possible Banti's disease. She suffered a spontaneous rupture of the spleen; splenectomy was done and the patient went to term. McKenzie (1936) recently reported a case in a gravida iii with a large mass in the left upper quadrant; the liver border was 5 cm. below the right costal margin; the uterus was the size of a two months' pregnancy. A diagnosis of splenic anemia with early Banti's disease was made. Splenectomy was done in the third month of pregnancy under spinal anesthesia. A scar in the liver was excised; the spleen weighed 1,100 gm. This patient made an uneventful recovery, went to term and delivered spontaneously. Malaria in pregnancy has been reported by Blacklock and Gordon, Buckingham, Clark, Deromps, Unger, Wickramasuriya and Wislocki.

*Read at a meeting of the Chicago Gynecological Society, November 20, 1936.

Banti's disease or splenic anemia has been defined as a primary disease of the spleen of unknown etiology, characterized by enlargement of that organ, anemia, tendency to hemorrhage and secondary cirrhosis of the liver, with jaundice and ascites. The spleen is the primary seat of the disease and in the later stages it is greatly enlarged. The splenic vein and the portal vein are also enlarged. Microscopically, there is marked fibrotic infiltration and Banti described a proliferation of the endothelial cells of the venous sinuses of the pulp, which he thought were characteristic of the disease. The disease is chronic and because of the decreased fragility of the red blood cells together with distended varices, hemorrhage may be a common feature. In addition to nosebleed, hemorrhage from the bowel, and hematuria—in women there may also be metrorrhagia. Jaundice occurs when there is liver involvement. Pregnancy aggravates the disease although the reverse does not seem to be true. Both medical and surgical measures must be instituted if the pregnancy is to be successfully terminated, as well as to improve the patient's general condition. In the nonpregnant state, early splenectomy followed by blood transfusion is the best treatment. The same medical and surgical principles may be

Fig. 1.—Case 1. Section of spleen (low power). Lymphoid follicles sharply demarcated. Marked proliferation of lymphoid elements in adjacent pulp. Sinusoids packed with red blood cells; increase in fibrous connective tissue throughout parenchyma.

followed during pregnancy. Where the disease has become chronic and severely aggravated by pregnancy even radical treatment may fail. Although the cases herewith reported terminated fatally, there seemed to be improvement for a short time following splenectomy, and these cases proved the deleterious effect of pregnancy upon the disease.

CASE 1.—M. W., aged thirty-three, gravida iv, white; admitted Feb. 17, 1935, complaining of an abdominal mass and amenorrhea. There was slight nausea and vomiting which was of recent origin. For the past two years the patient had been in good health. Family history irrelevant; there were three previous pregnancies, the last two of which were terminated by induced abortion, 1931 and 1932. Last period Nov. 22, 1934. Sclera slightly icteric, no lymphadenopathy, mass in abdomen occupying entire left upper quadrant 20 cm. below seventh costal cartilage. Notch felt in spleen, mass in right upper quadrant extending 3 cm. below the costal margin. No ascites. Wassermann negative. Blood pressure 116/70. By careful differential diagnosis, it was decided that the enlargement of the spleen and liver

was due to Banti's disease. Feb. 25, 1935, Aschheim-Zondek test strongly positive. Mar. 21, 1935, transfusion of 450 c.c. citrated blood. Mar. 23, 1935, splenectomy done under ethylene ether anesthesia. Liver and spleen both enlarged. The patient made a fair recovery and was discharged on the twenty-sixth postoperative day.

Pathologic Report: Spleen weighed 800 gm. and measured 22 by 11.5 by 7 cm. Microscopic: diffuse hyperplasia of endothelial tissue and fibrous tissue; lymphoid follicles increased.

Obstetric History.—On Aug. 8, 1935, patient was readmitted in labor about three weeks before term. Labor was irregular for a period of about four days. August 12, patient delivered spontaneously; O. L. A., stillborn fetus, weight 5 pounds 4 ounces. Ether anesthesia. The patient received infundin and ergot, each 1 c.c.; there was no postpartum hemorrhage. The patient was afebrile for eight days following delivery but on August 19 had a temperature of 101° F. and complained of numbness of the left hand and arm. Later in the day the left facial muscles were paralyzed; this was followed by paralysis of the left arm and left leg. Blood pressure 182/100. Provisional diagnosis, cerebral hemorrhage or embolus. August 20, 50 c.c. of 50 per cent glucose was given intravenously to relieve the cerebral edema. August 24, pain in the left chest; intranasal oxygen was given. August 25, patient had a definite pneumonia, the left upper lobe being entirely consolidated; she was cyanotic and dyspneic. September 1, severe pain in left leg; great toe discolored. It was believed that there was a thrombus in the popliteal artery of the left leg. September 8, patient became extremely cyanotic, the temperature reached 106.2° F., followed by death.

Postmortem.—Anatomic diagnosis: necrotizing endometritis following parturition. Thrombosis of uterine, internal, and common iliac veins and inferior vena cava. Embolism of both rami of pulmonary artery. Mural thrombi of right atrium, auricular appendage, and ventricle. Multiple hemorrhagic infarcts of lungs. Bilateral hypostatic pneumonia and pulmonary edema. Embolism of left common iliac artery and thrombosis of left femoral vein. Edema and gangrene of left lower extremity. Cerebral embolism. Bilateral fibrous pleurisy with complete obliteration of right pleural cavity. Moderate hypertrophy of left ventricle. Healed calcareous tubercle of right upper pulmonary lobe. Spleen absent, fibrous adhesions of the peritoneum and thrombosis of the splenic artery and vein. Liver weighed 1,930 gm.

CASE 2.—L. R., aged twenty-three, gravida ii, white; admitted Oct. 19, 1935, complaining of abdominal pain. In July previous the patient had had a splenectomy in the fourth month of pregnancy. Her last pregnancy (1934) had been terminated by therapeutic abortion because of an enlarged spleen. On her second admission to the hospital, she was six and one-half months pregnant, and because of the severe anemia it was decided to empty the uterus, by the insertion of a bag under ethylene anesthesia (Oct. 29, 1935). After twenty-four hours the bag was removed, the anterior lip of the cervix was incised and the baby delivered by version and extraction. It weighed 3 pounds 12 ounces, and lived about one-half hour. November 17, left leg edematous and painful; thrombophlebitis. November 30, abdominal distress and ascites; December 4, ascites increasing; edema of right leg. December 12, paracentesis, 5,000 c.c. of straw-colored fluid removed from abdomen. December 23, ascites, dyspnea; 3,000 c.c. clear straw-colored fluid removed from abdomen. Jan. 14, 1936, omentum attached to rectus sheath; less distention; patient also given a 500 c.c. blood transfusion. The patient was discharged January 15. She was worse on discharge, and died at home one week later. No autopsy.

Malaria complicating pregnancy is rare in this part of the country.

CASE 3.—M. B., aged thirty, gravida ii, white, a native of Arkansas. In May, 1933, the patient was treated for malaria with quinine. Since then she had had an increasing tumor of the abdomen. She reported to the dispensary complaining of a mass in the abdomen and amenorrhea. Vaginal examination revealed a uterus the size of a four months' pregnancy, distinct from the tumor which was in the left upper quadrant. The patient entered the hospital on May 10, 1935, with a diagnosis of pregnancy complicated by an enlarged spleen. After much debate it was decided to do a splenectomy because of the increasing size of the abdomen. She was given a blood transfusion followed by splenectomy. She made an uneventful recovery and was discharged on the twelfth postoperative day. The spleen weighed 1,200 gm. Microscopic diagnosis, fibrous splenitis, typical of malaria. On Oct. 24, 1935, patient entered the hospital in labor. She was about three weeks past term. Fetus in O. D. A. position. Labor lasted seven hours; low forceps delivery. The baby weighed 3,655 gm. Puerperium afebrile. Patient was discharged on tenth postpartum day. Mother and baby apparently normal.

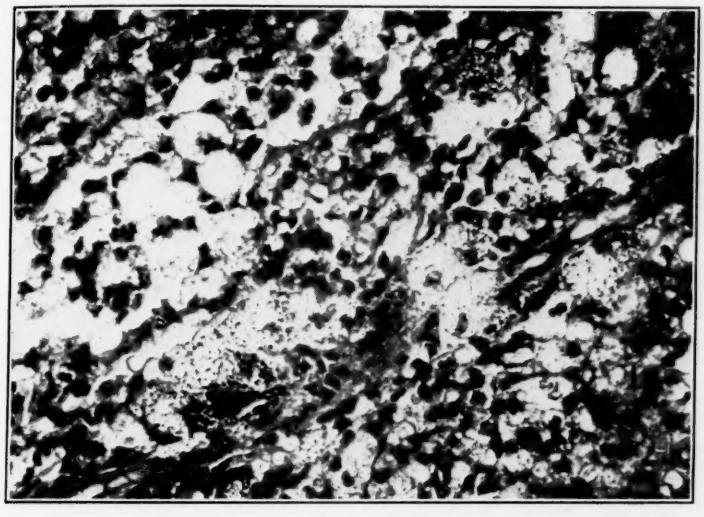

Fig. 2.—Case 3. Section of spleen. Accumulations of fine dustlike pigment within the reticulo-endothelial phagocytes. Sinusoids filled with red blood cells, and increase of fibrous connective tissue.

COMMENT

During normal pregnancy the spleen does not undergo any appreciable hypertrophy. Any enlargement during pregnancy is usually due to preexisting disease, as in the three cases reported here. A moderately enlarged spleen weighing up to 800 gm. may not be disturbing in pregnancy. A spleen weighing 1,000 gm. or over constitutes some embarrassment and is an impediment to a growing uterus. In addition, the pregnancy may be a factor which might aggravate the disease. In cases of Banti's disease, preliminary medical therapy and transfusion followed by splenectomy is good treatment. The latter, when carried out early, may be life-saving. X-ray irradiation over the splenic area has been employed, but its intensive use is not recommended during pregnancy.

In the cases reported here, pregnancy was followed by some improvement after splenectomy; the literature reveals other patients who went to term and had normal labors and normal babies following splenectomy.

Chronic malaria with enlargement of the spleen is not usually considered an indication for splenectomy. In our case, the enlarged spleen of 1,200 gm. gave rise to persistent pain as the uterus increased in size. After careful deliberation, it was decided to remove the organ and the patient's convalescence, subsequent pregnancy, and labor were uneventful. However, quinine therapy may be instituted with safety, even in large doses, to prevent malarial intoxication, abortion, stillbirth or transmission of malaria to the fetus. The puerperium is a critical period inasmuch as a recurrence during this period, followed by chills and fever, may be mistaken for puerperal sepsis. Blood smears should be made to differentiate puerperal malaria from puerperal sepsis.

SUMMARY

1. Three cases of splenomegaly during pregnancy are reported, two of Banti's disease and one of chronic malaria.

2. Banti's disease is aggravated by pregnancy. Preliminary transfusion followed by early splenectomy may be safely undertaken in the pregnant as well as in the nonpregnant state.

3. Enlarged spleen in chronic malaria may call for splenectomy because of its size to permit room for uterine growth. Quinine therapy may be instituted for treatment of malaria during pregnancy to prevent abortion, stillbirth, and transmission to the fetus, or its recurrence during pregnancy or the puerperium.

4. Splenic tumor must be differentiated from other abdominal tumors during pregnancy, particularly ovarian tumors and fibroids.

I wish to thank Drs. Saphir, Strasser and Lotspiech for their help in preparing the slides and photographs.

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30 North Michigan Avenue

EPISACROILIAC LIPOMA*

Emil Ries, M.D., Chicago, Ill.

(From the Gynecologic Department of Post-Graduate Hospital and Medical School)

THE observation of an apparently unique case and the investigation which it caused me to make has led to the establishment of a clinical and pathologic unit which appears to be new and undescribed in medical literature. Its connection with the symptom of backache must make it of great practical importance.

Mrs. N. K., thirty years old, white, American, hotel worker, operated upon for tubal pregnancy in 1917, for left salpingitis, hemorrhoids and fistula-in-ano in 1929, came for examination April 29, 1936, on account of disabling pain in the back extending to the right hip and thigh which woke her up in the morning and lasted all day. It was increased by bending over. She also complained of painful menses with discharge of clots, leucorrhea, headaches, constipation, varicose veins in both legs which were painful at times.

*Reported at a meeting of the Chicago Gynecological Society, October 23, 1936.

Examination showed: Weight 172 pounds. Hyperplastic sinusitis, deflected septum, dental pyorrhea, buried infected tonsils. Chest without pathologic findings. Upper abdomen without findings. Corneal, pharyngeal, patellar, pupillary reflexes normal. There was no infection of the urethra or labial glands. A small fibroid was found in the body of the uterus, otherwise the genitalia were normal. Fistula-in-ano well healed. Blood Wassermann and Kahn negative. Urine normal.

Examination of the sacral region showed a 3 by 2 cm. elliptical tender tumor placed transversely over the lower end of the right sacroiliac joint at about the point of the lateral dimple. It was elastic and of the consistency of a fatty tumor. A smaller tumor, also tender, was found over a symmetrical point on the left side. The patient declared these tumors to be the seat of her pain in the back. On repeated examination the patient located her backache consistently at these two points.

May 20, 1936, the tumors were removed through two small incisions with practically no loss of blood. Under the tumors the periosteum of the sacrum was seen and felt bare. A few linen skin sutures and a compression dressing finished the operation. (For microscopic findings see under "pathology.")

The patient reported freedom from pain at once. Absence of pain in this area was reported repeatedly up to October, 1936.

On account of the location of the tumors and their microscopic diagnosis (see "pathology") I designated them as episacroiliac lipomas.

No previous report of this group of tumors has been found in the literature.

With the cooperation of my associate, Dr. Richard Lifvendahl, I undertook the examination of 1,000 persons at random in dispensaries, hospitals, and otherwise, in order to find whether similar cases existed and had been overlooked.*

We have examined 250 males and 750 females. Out of the 1,000 persons examined, 309 had backache in the lumbosacral region; 159 of these were without any tumors. But among the 1,000 examined, 317 had tumors similar to the ones reported above, a ratio of 31.7 per cent. Of the 317 with tumors, 46 were males, 271 females, that is: 18.4 per cent of the males examined and 36.1 per cent of the females examined showed tumors. The small proportion of males examined may well cause the apparent difference. Of the 317 with tumors, 223 were white and 94 colored. Of the 317 with tumors, 150 complained of backache, 167 had no backache. In 131 of the 317, the tumors were spontaneously painful, in 186 the tumors were not painful. In 231 of the 317, the tumors were bilateral, in 86 unilateral.

The age distribution of the 317 with tumors is as follows: under ten, 7; to twenty, 13; to thirty, 67; to forty, 102; to fifty, 80; to sixty, 29; above sixty, 19.

Forty pregnant women were examined and showed the following ratios: 22 had tumors, 14 had tumors and no pain, and 4 had episacroiliac lipomas and pain in them.

It was found that fat patients were as often without tumors as thin ones showed positive findings.

I wish to emphasize that not the remotest connection with the "adiposis dolorosa" of Dercum has been uncovered.

Small lipomas in other parts of the body of persons examined partially were found in two cases out of the 1,000, but complete examination of the entire body was not carried out in the entire series.

The examination is carried out with the subject sitting on an examination table bending forward or lying on one or the other side with the sacral region

*Our thanks are due to the staff of Postgraduate Hospital and Medical School, Dr. H. Tumpeer of the Allergic Clinic of Michael Reese Hospital and to the Gynecologic and Obstetric Dispensary of the Medical School of The University of Illinois (Professor Falls) for facilities extended.

exposed. The tips of the examiner's fingers pass over the entire sacral and the neighboring iliac regions. The posterior sacral surface having many irregularities, it is necessary to exclude bony prominences. Therefore, no tumors are counted as positive which cannot be moved freely.

If the tumor is declared sensitive to touch by the patient, the examination is directed to the surrounding territory and brought back to the sensitive area. No tumor is put into the category of "sensitive" unless the patient identifies the area positively on repeated palpation.

Symptomatology.—A great number of persons have backache, but no episacroiliac lipomas (159 out of 1,000 examined). A great number of persons have such tumors, but have neither backache nor sensitiveness or spontaneous pain in them and are perfectly positive on this point (167 out of 1,000 examined).

But it is a most striking experience to hear a patient who has gone through the whole gamut of medical, gynecologic and orthopedic treatments including drugs, serums, vaccines, plaster-casts, diathermy, etc. exclaim emphatically "that is the point" when his episacroiliac lipoma is touched in the examination. Patients with these painful tumors recognize the area as the seat of their pain immediately, and the pain is elicited promptly by handling, pressing, or moving the tumor.

In some patients pressure on the episacroiliac lipoma is not only painful, but causes pain to radiate from the tumor in different directions.

In the majority of persons with episacroiliac lipomas the tumor would never have been suspected unless a systematic search, such as we carried out, had revealed it.

Since we have carried our investigation into several clinics, the physicians connected with them have had no difficulty in finding episacroiliac lipomas on their own patients independently.

The shape of the tumors is cylindroid or round. The cylindroids are practically always placed transversely. The consistency is that of a more or less elastic lipoma, sometimes that of a soft fibroma. The largest size found so far was that of a silver dollar and as thick as the little finger. The smallest has been no larger than about 1 cm. in diameter. The skin is always movable over the tumors, so much so that a spectator at the examination can see the tumor slip under the skin. The character of the pain is mostly described by the patient as an "ache." Backaches are located in many different regions of the back, but those due to the tumors described here are limited in extent to the neighborhood of the sacroiliac joint, though they may radiate slightly.

Location.—The two characteristic dimples in the sacral region are the most favored sites of these growths. Most of those we have found were within 5 cm. of either dimple. The mobility of the tumor is limited, but distinct. We have found only one patient, aged seventy, whose two tumors could be moved across the midline, where ordinarily the skin has bony attachment. This patient had disk-shaped tumors on each side, the circumference of a silver dollar and the thickness of a little finger. She had no pain in the tumors and was under treatment for cystitis.

In most cases the growths are symmetrical and of similar shape on both sides. In a few one side is larger than the other. Fewer persons are positive only on one side. In very rare cases we have found more than two, as high as four and six, arranged symmetrically in vertical rows over the sacroiliac joint. The patient with four had enough backache to handicap her in her work. The one with six tumors had no backache.

Duration.—None of the persons examined (except the three noted below) had any knowledge of their tumors and therefore none could give us information about the length of time they had had them. But if the symptom of severe backache

which was referred to the episacroiliac tumors can be taken as guide, these patients at least had suffered from them for years.

Dr. Lifvendahl has found three patients who knew of their tumors:

A woman, forty-six years old, under gynecologic treatment for two years without improvement, pointed out a tumor over the sacrum. Two episacroiliac lipomas were found on examination, one was removed and one injected with novocaine. Backache was reported absent two weeks later.

A woman, twenty-eight years old, with backache for two months, knew she had tumors over the sacrum. Two were found.

A woman of seventy-two years knew she had a "knot" over the right side of the sacrum for five years and pain in the right side of her back for five years. Two episacroiliac lipomas were found, the right one painful to the touch. The left one was larger, but only slightly tender. No treatment was given.

Treatment and Results.—The treatment of the episacroiliac lipomas has been by injection or by excision.

Fig. 1.—Episacroiliac lipoma. *F*, fat cells. *N*, nerve. *V*, blood vessel.

Injection of 2 per cent novocaine with or without adrenalin into the tumor or around and under it has been a simple way of relieving the pain. The relief has been strikingly rapid, especially in cases of long standing and which have had many kinds of other treatments. It has happened repeatedly that patients who moved bent over and with great distress, straightened out immediately and declared themselves comfortable after the injection. This change would not be deserving of attention, if it were of no longer duration than the usual effect of the injection of a local anesthetic. But the result in a number of cases has endured now for weeks.

In the case of rather large tumors or where injection of novocaine has relieved only temporarily, the tumor or tumors have been excised, usually under local anesthesia. It has always been a simple matter to peel out the tumor from the surrounding tissue and there is very little bleeding. The fact that the tumor shells out deserves emphasis.

Some twenty patients have so far been treated surgically by excision or injection of novocaine. The time is too short to report on remote results. Some patients have been relieved at once and have remained free from pain and disability. In others pain in near-by areas or in the area injected has returned more or less. In the first case reported here, pain is complained of, but not in the region where the tumor had been located, but higher up and this patient had a fibroid of the uterus, sinusitis, infected tonsils, deflected septum of the nose, pyorrhea, which she had not yet had taken care of. The original site of the tumors was painless and the patient was working (October, 1936).

Pathology.—The episacroiliac tumors are more or less rounded cylindroids. They have a distinct fibrous capsule and are perfectly smooth on the surface. The cut section shows fat tissue.

Microscopically they consist of fat tissue with very little connective tissue between the fat cells, while the capsule consisted of a little more dense fibrous tissue.

In one case, microscopically a small nerve has been found running through the middle of the tumor (Fig. 1).

The relation of the lipomas described here to neurolipomas is still under investigation.

Conclusion.—A previously undescribed clinical group of lipomas in a special location over the sacroiliac joints is established, to which the name "episacroiliac lipoma" may properly be applied.

The connection of this group of tumors with backaches, their surgical treatment and its results deserve wider attention.

Investigation of the relation to neurolipoma requires more extensive material.

2400 Dearborn Street.

ANGIOMATOSIS RETINAE (VON HIPPEL'S DISEASE, LINDAU'S DISEASE) COMPLICATED BY PREGNANCY*

Mervyn V. Armstrong, M.D., F.A.C.S., Brooklyn, N. Y.

(From the Department of Obstetrics and Gynecology, Long Island College Hospital)

THIS case seems worthy of record, because of the extreme rarity of the condition. It is the second case recorded in the literature, in which pregnancy was noted as a complication and is the first for which cesarean section was performed, with angiomatosis retinae as the sole indication.

Angiomatosis retinae is a disease characterized by immense dilatation and tortuosity of retinal vessels and the development of angiomas usually toward the peripheral retina (von Hippel's disease). It is frequently associated with angiomatous cysts of the brain and spinal cord, and malformations or cysts of various somatic organs. When this association is present, the condition is known as Lindau's disease.

Mrs. M. B., twenty-two years of age, was admitted to the prenatal clinic of the Long Island College Hospital, Jan. 4, 1936, complaining of disturbance of vision and amenorrhea of five and a half months' duration. The medical and surgical history was essentially negative. Menstruation began at thirteen, recurred regularly every twenty-eight days, of four to five days' duration and not painful. This was her first pregnancy. The last period occurred on July 7, 1935, and quickening was noted on Dec. 15, 1935. The estimated date of confinement was April 14, 1936.

The visual disturbance dates from 1930, when the patient was sixteen years old, and attending high school. During routine physical examination in school,

*Presented at a meeting of the Brooklyn Gynecological Society, December 4, 1936.

vision in her left eye was found to be poor. She went to an optometrist, who was unable to benefit her with glasses. She then was referred to the Brooklyn Eye and Ear Hospital, where a diagnosis of angiomatosis retinae was made.

Therapy consisted of intravenous salvarsan, tuberculin, calcium gluconate and x-ray treatment to the head. During the past six years there have been frequent physical and special neurologic examinations, including Barony equilibrium tests and x-ray examination of head and abdominal organs. In less than one year after the onset of visual disturbance in the left eye, the vision in the right eye began to diminish. Vision has become markedly impaired to date, so that at present, the patient can only distinguish between light and darkness. Her eyegrounds have been examined, not only by practically all the members of the staff of the Brooklyn Eye and Ear Hospital, but she was also demonstrated before the New York Ophthalmological Society, The Eye Section of the American College of Surgeons, and the Eye Section of the New York Academy of Medicine.

The patient was admitted to the obstetric ward of the Long Island College Hospital on April 1, 1936, at which time her general physical examination was essentially negative. The pelvic measurements were normal. The uterus was enlarged to size of full-term pregnancy and the fetus was lying in L. O. A. The fetal heart was 140 and regular. Pelvic examination was omitted because cesarean section was being considered. Her blood pressure was 110/60 and the urine, blood count, chemistry, and Wassermann were negative.

The opthalmologic findings by Dr. Evans on April 3, 1936, were as follows:

Left eye showed secondary cataract, with synechia from a quiescent iris, binding the border of the pupil to the capsule of the lens. The episcleral vessels were slightly congested. The cornea was clear; the anterior chamber shallow. Tension normal.

Right eye showed external structures without evident pathologic changes, nor was there any pathology in the anterior chamber, iris, or lens. A few small vitreous opacities could be seen floating about with movements of the eye. The optic disc was elevated about one diopter, was pink in color and had blurred edges. Emerging from its center were a number of tremendously dilated and tortuous blood vessels. These were most noteworthy passing temporally, where toward the midperiphery, two of them merged in a large, elevated, round mass which was apparently made up of a medusa-like collection of small blood vessels. About these vessels was a translucent zone, which was suggestive of a cyst wall and the adjacent retina was apparently distended and thickened, by the formation of innumerable minute cysts, which suggested the appearance of soapy foam.

As the greatly distended and thickened vessels leave the nerve head, they are accompanied by wide bands of yellowish "snow-bank" exudate. The two greatly dilated vessels extending from the nerve head and running upward and forward toward the nasal periphery were partly obscured by a fold of detached retina, and though their terminations could not be seen, they doubtless ended in a second angioma. Throughout the eyeground occasional small hemorrhages and scattered spots of old and new exudate were noted. The tension was 23 mm. of mercury (McLean). Visual acuity was 10/200.

As a result of this opthalmologic consultation with Dr. John N. Evans, cesarean section under local anesthesia was deemed advisable. Dr. Evans felt that the already dilated and diseased vessels might not withstand the marked vascular strain, that inevitably accompanies spontaneous labor. The fact that there might be an associated lesion elsewhere in the central nervous system, or in one of the parenchymatous organs also was considered.

On April 9, 1936, a classical section was performed under local anesthesia and the patient was delivered of a normal living male infant weighing 2,940 gm. Sterilization was recommended, but consent was refused by her husband. The postoperative course was uneventful and the patient was discharged from the hospital on April 26, 1936, seventeen days after operation.

SUMMARY

1. A case of angiomatosis retinae (von Hippel's disease) has been presented.

2. A careful survey of the literature shows that this is the second case of this disease complicated by pregnancy.

3. This is the first case on record, in which angiomatosis retinae has been accepted as an indication for cesarean section.

4. While up to the present time, there is no definite evidence of an associated Lindau's syndrome in this patient, cases of this type should be followed by both x-ray and physical examination for evidence of pathology in the central nervous system or somatic organs.

The author is deeply indebted to Drs. John N. Evans and Ralph I. Lloyd for their assistance and suggestions in the preparation of this case report.

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85 PIERREPONT STREET

DISCUSSION

DR. HAROLD F. SCHILBACK.—The story of this patient is typical. These cases come to us because there is an insidious loss of vision. The first objective finding is a dilatation of one vein. Shortly afterward there is a dilatation of the artery which accompanies that vein. Usually, the dilatation is particularly noted in two vessels and these may be, as in this case, in the upper temporal area. Shortly following the dilatation we, of course, get exudate both in the retina and beneath it. Later, hemorrhages occur. With the resolution of the exudate, one finds most frequently detachment of the retina because of a retinitis proliferans. As has been said, this patient undoubtedly will go on to complete blindness, because the right eye, with the retinal detachment, is now very much involved.

Frequently a complication arises in these cases whereby there is, on some physical effort, a spontaneous hemorrhage. With that there is, of course, an acute glaucoma. The vessels are extremely large, bleeding is great, and there is very little that can be done about it. You cannot operate for the relief of the glaucoma because that is followed by more bleeding. The patient is in severe pain and the loss of vision is prompt. To avoid such an accident the procedure which has been noted was undertaken.

ECTOPIC GESTATION FOLLOWING POMEROY STERILIZATION*

MARTIN H. LUTZ, A.B., M.D., BROOKLYN, N. Y.

THIS case is one of a pregnancy, extrauterine, following attempted sterilization by the Pomeroy method.

Mrs. V., a thirty-one-year-old multigravida, was operated upon by me at the Peck Memorial Hospital, Brooklyn, March 12, 1935. The preoperative diagnosis was eight weeks' gestation, complicated by early malignant hypertension, established by her past history as well as the physical findings.

Operation, March, 1935, abdominal hysterotomy and bilateral tubal resection (Pomeroy method). At the time no gross tubal or peritubal pathology was noted. The fallopian tubes were grasped by Allis clamps at approximately their midpoints and a liberal portion, about 4 cm., of the mid-section of each tube was removed. The base of the tubal loop produced by traction on the Allis clamps was ligated as usual by a chromic No. 1 ligature. The patient's postoperative course was uncomplicated, her abdominal wound healed by primary union. Histologic examination of the structures showed no abnormalities.

Approximately one and one-half years later, September, 1936, this patient was reoperated upon by me at the Peck Memorial Hospital. At this time the preoperative diagnosis was right ectopic gestation. The pelvic findings at the time of this operation were as follows: The distal portion of the right tube was the site of a "tubal abortion," so-called. There was moderate hemorrhage into the abdomen. The portion of the right tube involved in the gestation and the right ovary were removed. The proximal or uterine portion of the right tube was resected. Inspection of the left tube showed a separation in its mid-section and adhesions to the sigmoid. Future pregnancy did not seem possible by way of the left tube. Operation was limited to removal of the distal portion of the right tube and the right ovary. Histologic examination of the tubal tissue confirmed the diagnosis of extrauterine gestation. The patient's postoperative recovery was uneventful.

47 PLAZA STREET

DISCUSSION

DR. GEORGE H. DAVIS.—At the Methodist Episcopal Hospital we have had two failures following the Pomeroy sterilization. However, in deference to the method, I must state that in both of those cases, the tubes were tied off with chromic catgut, rather than with plain catgut, as used at the Brooklyn Hospital.

Lately we have been burying the proximal stump of the tube and thus far we have not had any reported subsequent pregnancies. The ease with which this is done depends on how close you tie the tube to the uterus. The stump can be buried very easily, either by a purse-string suture, or between the layers of the broad ligament. It takes only a few additional seconds for each tube, and I do not believe any recurrences will follow.

DR. THURSTON S. WELTON.—I know that Dr. Pomeroy used plain catgut sutures, but I believe that either black or white silk is more satisfactory.

*Read (by invitation) at a meeting of the Brooklyn Gynecological Society, December 4, 1936.

DR. ALFRED C. BECK.—I am interested in knowing how the spermatozoa entered the tube. Do you think that they entered from the side of the ectopic or did they cross in the abdomen from the opposite tube?

DR. WILLIAM F. NELMS.—We have been using this method of sterilization at the Brooklyn Hospital for the last fifteen years. We have done 219 cases and have had no reported cases of pregnancy. Dr. Lull, of Philadelphia, tried it out on 223 cases and states he has had no failures reported from a 72 per cent follow-up.

We believe that one of the reasons why this method has been satisfactory in our hands is that we do not produce too much trauma. If too much trauma is produced to the tube either by crushing or the use of nonabsorbable sutures, necrosis results, and it is much more likely to break down and form a fistula.

There are one or two other points in the technic that we use which might be referred to. We do not make so large a loop that when it is ligated too much tension is exerted on the tube. With a large loop the ligature is liable to slip off or cut through the stump. The same thing applies when the loop is made too close to the uterus. Especially in conjunction with cesarean section where there is a large pregnant uterus, if the loop is made near the uterus, and not in the middle portion of the tube, the weight of the uterus moving from one side to another and in involuting, is likely to cause the ligature to cut through.

We have had but one complication in our 219 cases and that was a case of intestinal obstruction that developed about three weeks after the operation. On opening the abdomen in that case we found a loop of bowel adherent to the cut ends of the tube, and on freeing the adhesions around it, there was an escape of one or two drops of pus.

DR. WILLIAM SIDNEY SMITH.—In answer to Dr. Welton, I would like to say that Dr. Pomeroy never used black silk as a ligature in his method of sterilization. He avoided a nonabsorbable suture for the reason that it is liable to leave a fistula. He always used either plain catgut or No. 1 chromic catgut.

DR. LUTZ (closing).—Dr. Beck has asked how the spermatozoon reached the ovum to fertilize it. The right tube had a definite separation midway between its proximal and distal portions where part of it had been resected during attempted Pomeroy sterilization. The cut end of the fimbric segment of the tube was apparently closed by an adhesion. Therefore, I believe the spermatozoon must have traveled through the uterine portion of the severed right tube, reached the abdominal cavity and found its way to the ovum and fertilized it near or at the fimbric portion of the tube.

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During the last 10 to 12 years, Mayer has punctured the amniotic sac through the abdomen in 12 cases of hydramnios. The indications were pressure symptoms including dyspnea. The technique is simple and the amount of fluid removed varied between 850 and 3,750 c.c. The immediate result was always good because the pressure symptoms subsided immediately. To prevent labor pains morphine and pantopon were given after the puncture. In five cases, however, labor followed in 1, 3, 6, 8, and 10 days respectively. There were no untoward effects encountered, although one patient fainted and vomited. No babies were injured. To avoid the placenta, punctures should not be employed in cases of placenta previa.

J. P. GREENHILL.

Symposium on Sterilization

EUGENIC STERILIZATION LAWS IN EUROPE*

MARIE E. KOPP, PH.D., LARCHMONT, N. Y.

STERILIZATION is a recent addition to the armamentarium of preventive medicine, and it is the United States which has pioneered in the development of eugenic sterilization for those unfit for procreation by virtue of severe hereditary afflictions, as the first statute in the world was enacted in the State of Indiana in 1907. There are now 28 states in the Union with a similar provision written into the statutes. America therefore served as example to the rest of the world.

Closer attention to the background of European laws, the oldest of which is but seven years old, reveals that sterilization was advised on eugenic and therapeutic grounds as far back as 1892 by Dr. August Forel in Zurich, Switzerland. Forel initiated the 1901 *Swiss Law for the Protection of the Insane and Feebleminded* which authorized physicians to employ whatever therapy they deemed necessary to improve a patient's condition.

In Germany, there were sterilization bills before the Prussian Legislature in 1903, before the Saxon Legislature in 1923, and before the Reichstag in 1907 and 1925. In addition, most of the preliminary work was completed for the enactment of the present sterilization law before the political upheaval occurred early in 1933. The first European law was passed in 1928 in the Swiss Canton de Vaud, and was followed in quick succession by Denmark in 1929, Germany in 1933, Sweden and Norway in 1934, in Finland and Danzig in 1935 and in Esthonia in 1936. The Swiss enactment was particularly noteworthy in view of the well-known Swiss opposition to legislative regulation.

In ten other countries sterilization on eugenic grounds has been or is being discussed before the legislatures, and enactment is expected in the near future.

The sponsorship of eugenic sterilization legislation in Europe emanated from each medical group, as the psychiatrists, obstetricians, public health officials, and from the social welfare boards.

The German law is based on thirty years of research in psychiatric genealogy under the leadership of Dr. Ernst Ruedin. The German Psychiatric Research Institute in Munich has undertaken extensive studies of the incidence of diseases believed to be hereditary in origin. A most fertile field for study has been the northern slopes in the Alpine region, Switzerland, Bavaria and western Austria, a well-known goiter area. It is on the basis of such investigations that the German Legislation specified the hereditary condition serving as indication for eugenic sterilization under the 1933 Law. These are the hereditary

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, November 24, 1936.

forms of feeblemindedness, schizophrenia, manic-depressive psychosis, epilepsy, and Huntington's chorea in the mental group; and deafness, blindness and severe hereditary bodily malformation in the physical group of diseases.

On the basis of a vast amount of case material gathered in Germany and elsewhere, Ruedin's prognostication of the probable recurrence of disease is illustrated in the following few samples. In the case of one parent affected by hereditary feeblemindedness, at least one child in three may be feebleminded, and only an exceptional issue will not be feebleminded if both parents are thus affected. Likewise he believed that 9 to 10 per cent of the issue of one schizophrenic parent may be schizophrenic, while 17 per cent will be the schizoid type of individual and 22 per cent may be affected by other types of abnormality. At least one-half of the offspring inherit the disease if both parents are schizophrenic and in addition nearly one-third of their issue will be schizoid individuals. In manic-depressive psychosis the incidence of recurrent disease when one parent is affected will be about one child in three and an additional one in six will be a cycloid psychopath and nearly one in eight will be affected by other types of abnormality. Studies from Sweden show that two out of five offspring of deaf-mutes inherit the disease from their parents.

Studies of this kind exemplify the type of factual data which underlie the recent sterilization legislation in Germany. Medical opinion here and abroad is divided on the validity of some of the assertions of Ruedin and his followers. Final judgment must await the gathering and presentation of factual data on a scale which will permit definitive conclusions.

The foregoing figures show clearly that the problem of the hereditary transmission of disease is a formidable one, which offers large scope for medical science. The proportion of individuals who, because of hereditary conditions, are unable through their own efforts to provide for themselves and their offspring is conservatively estimated at 3 per cent in any population. Such proportions reflect the continued inbreeding of persons afflicted with hereditary diseases and are accentuated by the emigration of more competent elements in the population to more favorable areas.

The proponents of European sterilization argue that propagation of the unfit can be prevented by no means other than sterilization, for this is the only reasonable and humane way to limit offspring without requiring the intelligent and voluntary cooperation of the parents. Intelligent voluntary cooperation, they say, is not to be expected of the great majority of persons thus afflicted. They also point out that the public is gradually coming to demand that physicians sterilize individuals for a variety of reasons which are not wholly medical. Under the criminal laws in most European countries, sterilization would be considered a mutilation of the body despite its having been performed at the patient's request. It has, in fact, recently resulted in the prosecution of physicians in Graz, Austria; in Offenbach, Germany, and in Bordeaux, France. It is held that the physician is entitled to legal protection. Those who favor sterilization point out that funds are required for the hospitalization of those suffering from severe hereditary diseases, and for the maintenance of their families. These are social costs upon the commonwealth, and are of sufficient magnitude to warrant an interest

in their reduction. Without expensive segregation, the unsterilized mental defective easily falls prey to unscrupulous individuals. There is, finally, the basic eugenic argument used by adherents of sterilization, that the quality of the population is subject to deterioration if the propagation of the hereditarily unfit is allowed to continue unchecked.

Such views have been sufficiently prevalent in Germany and in the Scandinavian countries to force the passage of sterilization legislation. Measures to "render a person unable to propagate" are to be undertaken in the interest of the "public good," in the wording of several of the laws. Hence, most of the laws are aimed at those hereditary diseases which seriously interfere with ability to provide for subsistence and to make the expected adjustments of modern life. In some countries the issuance of marriage licenses to epileptics, deaf-mutes and adult feebleminded, with a mental age of nine or less, is made conditional upon their previous sterilization. The German law limits the indications for sterilization to those specific disorders in which they believe that transmissions to offspring will result, except that it also includes habitual drunkenness. The latter is defined as a state of such persistent and severe alcoholism that the patient requires repeated institutionalization or imprisonment for his behavior while under the influence of alcohol. The severe physical malformations mentioned in the German legislation are those which seriously interfere with locomotion and those which are grossly offensive.

Some laws specify that only the individual with an "incurable" hereditary disorder, and whose progeny would in all probability be similarly afflicted, may be sterilized, while others assert that the "preventable" and not the "incurable" quality of a hereditary disease makes sterilization desirable. The proponents of sterilization argue that the most extreme cases of mental disease require institutionalization in any event, whether from the point of view of the individual or of the community, and hence do not need sterilization. In some countries only the individual technically a public charge comes under the provisions of the law. In others the outward manifestation of a hereditary disease and the ability to procreate determine the issue. In a third group, carriers of diseased genes in badly affected families, and persons affected with noninheritable diseases, can avail themselves of the provisions of the law.

While taking full account of the hereditary aspects of mental and physical diseases and abnormalities, the sterilization laws do not, as a rule, cover persons suffering from infectious diseases, or such asocial individuals as criminals and habitual paupers. Nor do they apply to those individuals whose mental and physical condition prevent their returning to life in the community and necessitate continued segregation. The sterilization of institutionalized individuals would be an unnecessary strain and expense, unless institutionalization failed to prevent procreation. In Germany the individual adjudicated unfit for procreation, who for religious and other reasons objects to sterilization, has the alternative of segregation for the period of his reproductive life and in a state-supervised institution. The age of puberty determines in most countries the lower age limit, while the upper age limit for women ranges from thirty-eight to forty-five and for men from sixty on.

The social-eugenic laws in Norway and Finland, and the criminal laws in Germany and Denmark contain legal provisions for the castration of

extreme sexual delinquents or persons of marked sexual abnormality, but this is a therapeutic measure which is utilized as a last resort when all others have failed.

Sterilization for therapeutic reasons on strictly medical grounds is left to the judgment and discretion of the attending physician. Only the German law provides that sterilization carried out for therapeutic reasons must be recorded at the District Public Health Office, as a safeguard in case of later manifestation of the hereditary disease against future action on the part of the state under the sterilization law.

Sterilization for the sake of convenience, that is, for humanitarian social and economic reasons, is legally recognized in some countries, while others characterize such an operation as a criminal offense on the part of both physician and patient. Where the law permits, therefore, the physician is free to grant a patient's request for sterilization on almost any reasonable ground.

The European machinery for sterilization has been planned to minimize the abuses of the legal right to perform the operation. The written application for sterilization may be made by the individual who desires sterilization, or by a guardian on behalf of a minor or an incompetent. Under the latter designation are included superintendents of public institutions for the feebleminded, the insane, and the criminal. In the Scandinavian countries and in Switzerland members of the petitioner's family may file the application, whereas under the German law this is not possible except in the case of a member of the family who has been appointed as legal guardian of a minor or an incompetent. This prohibition also extends to representatives of the state, e.g., the district attorney, the mayor, or any other representative of the domiciliary or municipal government.

Without exception the European laws stress the point that the applicant for sterilization on his own behalf, or on behalf of another person, must be thoroughly familiar with the character, purpose, and effects of the operation. The laws then require that the local medical officer make a careful study and report on the health of the petitioner, his mental development and hereditary background, the nature and course of the disease, the environmental circumstances and other contributing factors.

The European laws enacted to date emphasize the voluntary spirit with which it is desirable to have the petitioner make his application, submit to careful investigation, and follow out the decision made in his case.

However, the German law provides for the compulsory sterilization of those hereditary defectives who are unwilling or unable to seek sterilization, unless they choose segregation in state-supervised institutions. The law in each other country is compulsory only with respect to public charges who do not need permanent institutionalization on other grounds. A public charge as defined under the European civil laws is an individual whose partial or entire maintenance is defrayed from funds of the commonwealth of domicile or from that in which he holds rightful citizenship. Under the provisions of the Social Welfare Acts on the continent of Europe, collateral relatives can be held responsible for the cost of maintenance of a kin in the ascending or descending line, as well as for blood kin of first and second degree.

In charge of the investigation in each country is the Department of Public Health which is responsible for filing petitions for sterilization proceedings. The inidvidual decisions are made in the name of the commonwealth after independent referees and special witnesses have been heard. Thus the operating surgeon or gynecologist is relieved of the responsibility of decision under the eugenic provisions of the law.

In the Scandinavian countries and in Switzerland the authority for such decisions rests with the Departments of Public Health and Social Welfare, while in Germany it is in the hands of the specially constituted Hereditary Health Courts. Actual decisions are usually made by small boards, committees, or courts with four to six members: a lawyer familiar with the routine of the Family or Domestic Relations Courts; a psychiatrist; a physician trained in medical genetics; and one or more physicians from general practice or engaged in various specialties.

The German law provides that no medical, legal, or governmental official may serve on more than one body rendering decision on a given case. This stipulation has been drawn to prevent conspiracy against an individual. The sterilization proceedings and hearings are not public, and all relevant data are held confidential, since medical, legal, and governmental witnesses are obliged to divulge information without constraint. Failure to maintain secrecy is punishable by fine or imprisonment. Most of the European laws provide for appeals from the decisions made by the responsible authorities.

Sterilization operations must be performed in hospitals approved by the Department of Public Health. Such hospitals must not only be equipped with adequate facilities for operation, but must also be prepared to care for mental cases during the period of convalescence. Only surgeons and gynecologists licensed to practice as "specialists" in their fields are allowed to operate.

The sterilization laws customarily require that the operation follow the decision as soon as possible. The German legislation specifies that no person may be subjected to sterilization if the operation would endanger his life. It is partly for this reason that all admissions for sterilization are given thorough medical examinations and diagnostic laboratory tests. If the surgeon in charge of the hospital believes sterilization to be inadvisable because of previously undiscovered disease, or because the success of the operation might be jeopardized, the law permits a postponement of the operation.

The operative technique is determined by the surgeon, who is thus free to use the method most familiar to him. The law specifically states that the method of sterilization shall be operative, except that irradiation is upon special indication permitted for women over thirty-eight years of age. Legally, the operation is understood to be a severing, tying or occlusion of the vas deferens, or of the fallopian tubes, but not a removal or mutilation of any other parts of the reproductive system. The operation must not interfere with endocrine balance or with sex desire or response. In all European countries a written report on the method of operation, the course of convalescence, and on the subsequent mental and physical state of the patient must be filed by the surgeon with the Public Health Office.

In European medical and psychiatric circles it is argued that, with operative procedures conservatively limited to the severing, tying, or occlusion of the vas deferens or of the fallopian tubes, the after-effects

of the operation resemble those of physiologic sterility from disease or other causes. It is, therefore, believed that mental and physical disturbances are highly unlikely sequelae of sterilization, as it is being performed under the law.

The costs entailed by the sterilization proceedings, the operation and the hospitalization, are borne by the institution normally charged with the care of the defective individual. In Germany, all legal proceedings are the financial responsibility of the State; the charges for operation and hospitalization are paid by the individual, the sickness insurance fund, or by the Board of Public Welfare. The sickness insurance covers a minimum amount above which the individual is responsible. The cost of institutionalization in Germany of those individuals who object to sterilization on religious or other grounds must be paid by the individual, his family, or by friends, and is never paid by the State.

Reports on the application of the Danish law show that 127 individuals have been sterilized since 1929. In the Canton de Vaud, Switzerland, 48 operations were performed during ten years before the enactment of the law in 1928; from that date until January, 1935, 46 additional operations were performed. In other Swiss urban centers, where there is no restrictive legislation, such operations are more frequent. In Germany, since the law went into effect on Jan. 1, 1934, the 205 Hereditary Health Courts have adjudicated more than 200,000 candidates for sterilization. The vast difference in these figures, even on a per thousand of population basis, measures some of the difference among the various laws as regards the scope of their compulsory features.

Experience with sterilization has been altogether too limited to furnish a factual basis for discussing the relative merits of voluntary and compulsory sterilization.

Increasing urbanization and mobility of the people, resulting in the location of families in new surroundings where they are not known by their neighbors or by the authorities, present a serious problem. This is the fundamental reason for the much discussed and often resented legislative regulations of many personal matters.

Here I may add that sterilization of those deemed unfit for procreation because of hereditarily conditioned defects is only one part of a program to improve the competence and health of the people. The European legislation movement to make the issuance of a marriage license conditional upon prenuptial medical certification will be, it is believed, the most effective single educational measure to improve the health standards of the people.

67 Echo Lane

OPERATIVE METHODS OF STERILIZATION IN THE FEMALE*

ELIOT BISHOP, M.D., BROOKLYN, N. Y.

(From the Obstetric Service of the Brooklyn Hospital)

ASIDE from the indications, which I will not discuss, the subject of sterilization continues to be a moot point. Methods have been attempted since 1850, and I will refer you to the well-known works on sterilization and contraception for the history of this matter. However, in Eastman's article published in the autumn number of the *Journal of Contraception* and in Hyams' address before the American Association of Obstetricians and Gynecologists and Abdominal Surgeons two years ago and in a paper by W. F. Nelms and myself published some six or seven years ago, the best-known procedures are referred to.

One ideal of any method should be for a temporary period, as a time may occur in the life of many a woman who has been sterilized when she wishes, and justifiably, that what has been done could be undone. Twenty years ago Cary did some experimental work on a metal band of resilient consistency that could be snapped around a tube like the trouser clip for a bicyclist. He never carried this idea through any practical experiment however.

In the last few years, Sovak, on Holden's service at Bellevue Hospital, has done well with reconstructing the oviducts damaged by disease. Whether or not they have attempted any after elective sterilization, I do not know.

In most instances, however, sterilization is needed for permanence, so we will confine our discussion to the means of permanently preventing conception without resort to contraceptives. Another ideal is a procedure that can be carried out with no invalidism. Dickinson and Hyams each have attacked this problem with ingenuity. I have seen no figures of follow-up to tell what their results may be. Time, in addition to a large series of cases, is necessary for more than presumption as to its surety. Hyams needs a definite amount of apparatus that is not universally at hand. The amazing ability of a hollow muscular tube to regenerate itself makes one suspicious of the scar in the uterine horn. For reason of its safety, we hope that a reasonably long follow-up will prove the efficiency of this method. In many instances, the need for sterilization crystallizes itself when the abdomen is opened, or about to be, and at that time the abdominal attack is justified.

An elaborate procedure on a tube may develop annoying ooze of blood, especially in the presence of a pregnancy. It may also disturb the blood supply of the ovary with the possibility of cystic degeneration or cystoma formation.

There have been many attempts to destroy continuity of the fallopian tubes; resection and burying the stump, etc., have been done after several different methods, many taking time and open to the objection of producing bleeding. The most commonly used methods are: of Kohler,

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who loops the tube in its middle portion, ligates with silk sutures and cuts off the loop; of Peitman, who ligates the tube with silk in two places about 2 cm. apart, splits the peritoneum exposing the tube, excises a section of the tube between the ligatures and then sews the split peritoneum over this with fine silk sutures. He calls this, "subserous partial tubal extirpation"; of Rabinowitz, who does just a Peitman, except that he sews the ends of the cut tubes with silk and buries the uterine stump in the musculature of the uterus; of Planner, who ligates doubly with silk, cuts between the ligatures, sews the ends with silk and buries the uterine stump in the broad ligament; of Hofbauer, who cuts the tube, ligates the proximal end with silk and approximates the round and ovarian ligaments over the stump; of Madlener, who loops the tube, crushes it together with mesosalpinx and ligates the silk or catgut sutures; of Williams, whose routine method is to excise the proximal end of the tube from the uterine horn by a wedge-shaped incision, carefully closing the wound with fine sutures.

The late Dr. Hussey of Brooklyn had an ingenious and fairly simple method of ligating and cutting the tube. With the end of the ligature, he pulled the distal portion down between the leaves of the mesosalpinx in a reversing direction, then whipped this slit over with the same suture which was carried over to close the opening in the uterine horn. I did this a number of times but occasionally general venous ooze necessitated a salpingectomy.

If sterilization is to be done at the time of an early pregnancy, instead of hysterotomy and tubal resection hysterectomy has been advocated. It is somewhat more serious surgery and also the resultant lack of menstruation may unnecessarily produce mental depression. In the tuberculous, it is more to be considered, for among the workers in that field there is definite feeling that each menses brings on or adds to fever and patients do not do as well.

With all these in mind, Pomeroy sought for a simpler procedure and produced a modification of Madlener's method. Madlener crushed the base of a loop of tube and ligated with a silk suture. Pomeroy caught up a loop of tube in its most flaccid portion, ligated the base with absorbable suture and cut off the loop. His theory of this sterilization was that the peritoneal exudate thrown out would, after absorption of the catgut, make a serous barrier over each cut end. Its simplicity is perfectly obvious, and its safety lies in the factor of its short-time consumption and more particularly its lack of hemorrhage risk. In this audience of expert pelvic surgeons those two factors may be dismissed for discussion.

As to the *surety* of this operation, like all others, there has been debate. In our original report in 1929 no pregnancies had followed the procedure as done at the Brooklyn Hospital or the Methodist Hospital. To get experimental confirmation of our clinical results we used cats and guinea pigs under observation over several periods of "heat" and obtained no pregnancies. On opening the abdomen we found the same results that we did in human beings, a specimen of which I have tonight. Between the cut tubal ends there is nothing but a fibrous peritoneal band.

Lull of Philadelphia in 1935 made the most comprehensive review of results of this method. He condemned all others but had an open mind as to a better method if it could be found. He criticized the others

for pregnancies that had followed, and subsequent operation for ovarian cystic disease. Of 223 patients, he had a follow-up of 72 per cent with no pregnancies. However, here is a condition in which practically a 100 per cent of follow-up really exists, for if a pregnancy occurs, the patient immediately reports it to the operator, usually with vindiction!

A few cases have been brought to my attention, claiming failure. One was a patient at the Jewish Hospital of Brooklyn who had an ectopic pregnancy. Inquiry developed that the sterilization attack was not done by the Pomeroy technic. A similar report came from the Methodist Hospital, but I was unable to ascertain the details. Within a fortnight, however, there was reported from the Peck Memorial Hospital an ectopic pregnancy in a woman who had been operated upon by technique identical with ours, I feel quite certain. Kellogg of Boston reported two cases that he did in the course of cesarean sections; he filed elaborate studies of the histology of the removed tubes recovered at second operations. He and I are led to believe that he did not take up a long enough loop of the tube on one side or the other.

With the long series that Lull has reported, more than one hundred at the Brooklyn Hospital and possibly an equal number at the Methodist, and unknown cases from other institutions, I feel that, with inquiry, 500 cases could be found. With only one case of subsequent pregnancy, I believe that we have, for the present, the most satisfactory method, for it is simple, safe and as sure, at least, as is humanly possible.

STERILIZATION BY IRRADIATION*

IRA I. KAPLAN, B.Sc., M.D., NEW YORK, N. Y.

(From the Division of Cancer, Department of Hospitals, New York City and Radiation Therapy Department, Bellevue Hospital)

THE subject of sterilization of the female is of grave importance to the radiation therapist, because of the numerous conditions and lesions associated directly or indirectly with ovarian or uterine physiology which he is called upon to control by a modality that is a newcomer among the customary standardized therapeutic means heretofore employed.

Until the beginning of the twentieth century, surgery was the only means of sterilizing the female. Then closely following the discovery of x-ray and radium, therapists discovered the biologic possibilities of this radiant energy. At first only its destructive qualities were noted, but soon the positive biologic and physiologic effects of x-ray and radium to stimulate or destroy cellular activity were recognized.

In 1904 Halberstaedter[1] based on the work of Albers-Schoenberg[2] who was the first to produce aspermia in the males by x-ray and that of Bergonie and Tribondeau,[3] who formulated the law that immature cells and those in a state of active division are more sensitive to irradiation than are cells which have already attained their adult morphologic and physiologic character, reported his observations with reference to the selective action of x-rays on ovarian tissues, and this developed the logical basis for treatment of gynecologic conditions.

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Two methods were used by the early workers, one in which the x-rays were applied to one pelvic area which required treatment over a few weeks or several months and the other administering a massive x-ray dose at once. In 1920 Seitz and Wintz[5] established their ovarian dose, i.e., that dose of x-ray given through the pelvis which would suppress the menstrual function. The x-rays were administered in one dose through the pelvis directly over the ovarian areas.

Morton,[4] in the United States in 1903, was the first to report on x-ray treatment of fibroid uterus. Originally it was believed that irradiation effect on fibroids was due only to its suppressed ovarian function; today, however, we know that irradiation produces sterilization because it acts directly on the uterus in addition to its effect on the ovaries.

At present our method for sterilization of the female based upon the work of Béclere and Solomon[6] consists of x-ray therapy to the ovaries and uterus, applied through the anterior and posterior pelvis in divided doses over a period of several weeks or the insertion of a small quantity of radium into the uterine canal, which is left in place for several days. The divided dose method is more advantageous than the single massive dose because in this method ill effects on the patient of the large dose are avoided, menopausal symptoms appear more slowly, the effect is more certain; overdosage avoided, and the treatment plan and dose may be varied from time to time as the condition of the patient warrants.

Conditions in the female for which sterilization may be indicated can be classed, for convenience, in four large groups: (A) Medical, (B) surgical, (C) gynecological, and (D) social.

Sterilization follows as a necessity when treating malignancy of the generative tract.

I. *Reasons for Irradiation.*—Irradiation either by means of x-ray or radium is a positive, readily administered, harmless procedure for sterilizing the female. This procedure is the method of choice, because, when properly administered, there is no mortality and no morbidity. Sterilization by x-ray therapy does not necessitate hospitalization as is required for surgical procedures, which may often present innumerable, difficult conditions for the surgeon, while irradiation is often a simple procedure, presenting few difficulties and rarely any adverse sequelae.

Surgical methods, unless that of total extirpation of the reproductive organs, have occasionally been unsuccessful in achieving the final result, because it has been reported that pregnancies occasionally ensued after such procedures. Adequately delivered irradiation will assure the patient definite sterility.

II. *When to Select Irradiation.*—Assuming that the internist has decreed sterilization to be essential for the patient's welfare in a case with cardiorenal disease or diabetes, irradiation is an effective valuable therapeutic method, because one need not contend with operative shock, infection, bed confinement, and other operative exigencies.

Particular attention is called to pulmonary tuberculosis in females where pregnancy may severely delay recovery or even cause loss of life. Sterilization in such cases is most effective in giving the patient an opportunity to recover. Rather than risk a serious operative procedure when active advanced tuberculosis is present, irradiation certainly is the method of choice for sterilization. In young women with active tuberculosis, where sterilization is decided upon, irradiation may cause cessation of menstruation for only a year or two, and then permit its resumption when the diseased lung condition has been sufficiently ar-

rested.[7] This, to be sure, would be an ideal condition but, unfortunately, it cannot be promised in every instance, although it does occur in a sufficient number of cases to warrant it as a therapeutic measure of real worth.

In women with severe thyroid toxicosis with pregnancy contraindicated, irradiation because of its freedom from shock or other operative exigencies is the method of choice for sterilization.

In leucemia, sterilization by irradiation is the most effective method of treatment.

Although the hormonal relationship is still to be definitely and adequately established, we advise total sterilization in women of menstrual age who have carcinoma of the breast, especially when associated with bone metastases. This procedure is based upon the clinical observation over many years, that patients with breast malignancy, who were unfortunately permitted to go through a pregnancy, had a definite aggravation of the cancer. In recent years, the influence of the estrogenic and lactogenic hormones of the ovary and pituitary upon the breast tissue has been demonstrated by Taylor[8] experimentally and clinically. Therefore, when it has been decided to sterilize such a patient, rather than submit her to another operative procedure, it is advisable to recommend sterilization by means of irradiation.

Often we are confronted with the problem of a woman over forty-five years of age presenting symptoms suggestive of the climacteric, and serious enough to necessitate operative intervention, with hormone therapy proving valueless. In such conditions irradiation is effective and harmless in relieving these symptoms, especially the profuse metrorrhagia which sometimes characterizes such changes in the female.

When, in occasional instances, an endometriosis is encountered, irradiation can be administered to the ovaries, and thereby inhibit endometrial activity at the site of the neoplasm. This method is superior to operative removal of the tumor mass along with ovariectomy. With irradiation sterilization, there is no associated operative risk nor mortality.

III. *Methods and Technique.*—a. X-ray therapy is the most feasible method to employ for sterilization. Patients can be treated ambulatory with little distress and minimum amount of disturbance.

b. Radium therapy may be employed, but in most instances this requires hospitalization. X-ray therapy is the treatment of choice in such conditions where any type of surgical procedure is contraindicated, and therefore radium therapy, entailing the introduction of radium into the uterus, a surgical procedure, may not be employed.

c. In those conditions where patients are close to the menopause, in the case of thin patients and in those who for economic reasons cannot afford the necessary hospitalization required by radium therapy, it is better to employ x-ray therapy.

d. X-ray therapy is used for temporary sterilization in young women or where temporary amenorrhea is required for relief of local or general conditions, because of the greater ease in controlling the administered dosage. At present, we have definite physical means of measuring a specific unit of x-ray dosage under standard conditions.

The use of radium is advised where bleeding is profuse and there is immediate, urgent need to arrest hemorrhage, and where severe anemia

is present, contraindicating radical surgical procedures. But in young women radium is more likely to cause permanent destruction of the endometrium than does x-ray. In very obese women, x-ray is ineffective because an insufficient depth dose reaches the pelvic organs, and therefore direct radium application in the uterus is necessary to control the condition. In cases where adequate x-ray therapy has failed to effect the desired results, subsequent radium therapy is indicated.

In cases of young females with some general condition necessitating sterilization, irradiation is the method of choice. Assuming a case of tuberculosis, where it is hoped to arrest the chest lesion, temporary amenorrhea would be the ideal aim. In such instances, x-ray therapy alone is advised. Formerly, radium therapy was deemed preferable in young women, since small doses destroyed the endometrium, but spared the ovary to a great extent because of the protection offered by the distance of the uterine canal from the ovary. In our experiments, reported in 1936,[9] we determined that only about 24 per cent of the radium dose given in the uterus reaches the ovaries. However, whereas menstrual function has quite often been resumed after x-ray therapy, it is more likely to be permanently suppressed following radium therapy.

The effectiveness of irradiation depends upon:

1. *Age.*—The younger the patient, the less the permanency of sterilization, and the older the patient, the nearer she is to the menopause period, the more rapid and permanent the sterilization. Rubenfeld and Maggio,[10] based on the study of a large number of patients treated at Bellevue Hospital, determined the chance of resuming menstruation after irradiation to be, in the age group of twelve to eighteen years, 100 per cent, between the ages of thirty-three and thirty-nine, only 53 per cent and in patients over fifty-three years of age, 0 per cent. The age group between nineteen and thirty-two years usually resumes menstrual function in about 75 to 80 per cent of the cases treated.

2. *Method Employed and Intensity of Dose Administered.*—The more intense the x-ray therapy administered directly to the ovaries and uterus, the more permanent the results. In radium therapy, the amount of dosage, the thickness of the filter used, the length of time employed for the application—all these vary the effect of the irradiation. In our opinion, radium therapy when properly used will more positively sterilize the female than will x-rays. The more intense the given dose, the more positive the results.

3. *Physical Size.*—The stouter the patient, the less intense the radiation reaching the ovaries or uterus. A greater surface dose of x-ray is required in a stout person in order to increase the percentage of depth dose reaching the uterus and ovaries.

4. *Condition of the Pelvic Organs, and Pelvic Infection.*—Where the uterus is sclerotic and small and the ovaries fibrotic, the reaction to irradiation is slow. In multiple fibroids, the effectiveness of irradiation is much lessened because of the multiplicity of the lesion. Extraordinarily large fibroids are but slowly affected by irradiation, yet in many instances irradiation is most valuable for the treatment of large fibroids when surgery is contraindicated. The presence of marked pelvic infection prevents effective reaction on the ovaries and uterus until the inflammatory condition has subsided. In the presence of pelvic infection, pus tubes and pyometria intracavity radium therapy is contraindicated.

Complications.—These may be due to: (1) Condition within the patient, (2) errors in technique, and (3) untoward effects.

1. Occasionally, radium application is made in the uterus when an unrecognized latent pelvic infection is present, lighting up the infection with subsequent formation of salpingitis and, in some instances, peritonitis. An unrecognized pregnancy may be aborted or the embryo destroyed in utero with the formation of pyometritis.

2. Errors in technique may cause distressing or even fatal conditions. Too intensive a dose, or x-ray improperly administered, may result in superficial burns of the skin, epilation of pubic hair, telangiectasis, and fibrosis of the abdominal wall. In some instances intestinal disturbances, colitis or proctitis, may occur. These may sometimes be ulcerative in character.

Poor or careless technique when radium is inserted into the uterine canal may result in perforation of the uterus. Should this occur accidentally, the radium is withdrawn and the patient treated expectantly. If the radium procedure has been carried out under aseptic conditions, healing takes place without further disturbance. If the dose is too intense and the radium improperly applied, fistulas into the bladder or rectum may occur; proper placement of the radium applicators and careful packing of the vagina will militate against such sequelae.

3. In some cases, sterilization intended as a temporary measure may create permanent amenorrhea and sterility, and the patient should always be told of this possibility. In a few instances irradiation sterilization may result in a too rapid onset of the menopause. In such cases, irradiation over the pituitary may relieve the distressing symptoms associated with menopause changes.

Radiation Sickness.—No matter what method of irradiation is employed, radiation sickness, nausea, vomiting, and malaise, may occur in some cases. Its cause is not as yet understood nor is it known why it should occur in some patients and not in others. Dietetic control, citric acid fruit juices, calcium gluconate, liver extracts, sedatives such as luminal or nembutal, atropine and sodium bicarbonate, are all useful in treating this condition. In some instances, symptoms are so severe as to require rectal feedings or intravenous infusions. Roentgen sickness, though at times very distressing to the patient, is rarely fatal. It ceases with the conclusion of the irradiation.

CONCLUSIONS

When properly administered by an experienced and trained therapist, sterilization by irradiation is effective and at the same time produces no untoward effects. Occasionally, irradiation sickness may occur, requiring special attention, but this condition is relieved with cessation of the treatment. When radium is employed, proper surgical precautions are essential to prevent infection or perforation. Radium therapy must not be administered in the presence of adnexal infection.

In young women, sterilization may be permanent instead of temporary and in some cases sterilization by irradiation may not prove effective, requiring subsequent surgical procedures.

To obtain effective results, it is essential that irradiation sterilization be carried out only by those properly prepared by training and experience in the employment of x-ray and radium therapy.

Irradiation sterilization is of equal worth and effectiveness with surgery, without the latter's associated mortality and morbidity.

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55 East Eighty-Sixth Street

STERILIZATION FROM THE POINT OF VIEW OF THE OBSTETRICIAN AND GYNECOLOGIST*

B. P. Watson, M.D., New York, N. Y.

MY VIEWS on this subject can be best and most briefly expressed by presenting to you an analysis of the public ward cases in which sterilization has been carried out in the Sloane Hospital for Women during the past five years, 1931 to 1935 inclusive. During these years we have sterilized 172 women: 44 in 1931, 28 in 1932, 46 in 1933, 27 in 1934, and 27 in 1935. This gives an average of 34 per year. The average for the four years 1921 to 1924 was 13.6. It is thus evident that we are sterilizing more women today than we were ten and fifteen years ago.

The total number of deliveries in the public wards of the Sloane Hospital for Women averages 1,575 per year. This gives a case incidence for sterilization over the past five years of approximately 2.17 for every one hundred patients delivered.

Indications for Sterilization.—In 28 per cent of the cases the patients were sterilized primarily because it was not desirable that they be subjected to future cesarean sections. Thirteen per cent of the cases were from the gynecologic wards and sterilization accompanied a plastic operation. In 20.4 per cent sterilization was done because of toxemia of pregnancy, including nephritis and hypertension, and in 14.4 per cent because of heart disease. The heart disease in these cases was chiefly of the rheumatic valvular type, although a few cases of syphilitic heart disease and one case of congenital heart disease are included. In 8.4 per cent the indication was of a neuropsychiatric nature. Among these are included several cases of psychoneurosis, psychosis, mentally defective individuals, grand mal, one case of multiple sclerosis, and one of disseminated sclerosis. In 4.2 per cent tuberculosis of one sort or another was the indication. In 2.4 per cent it was diabetes. There were two cases of central nervous system syphilis. In the remaining cases there was a variety of indications; in two a previous nephrectomy had been

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done, two were cases of malnutrition and there was one of each of the following: nephrosis, recurrent nephrolithiasis, previous pyelonephritis, hydronephrosis, ulcer of stomach, stricture of rectum, anemia with splenomegaly, hyperemesis gravidarum with syphilis, recent pleurisy with syphilis, and obesity in a para viii. As will be stated later on, in all of these patients, there were other definite indications for a laparotomy.

In connection with these figures and in comparing them with statistics from other hospitals, it should be remembered that the Sloane Hospital is a voluntary and a teaching hospital, and that in selecting cases for admission, preference is given to those which exhibit some abnormality. The circumstances under which these 172 women were sterilized were as follows:

1. At the time of cesarean section in order to protect the patient from the risk of future sections, or from the risk entailed by future pregnancies, in the presence of some condition, such as heart disease, which rendered the first section necessary, 41 per cent.

2. Along with hysterotomy in patients in whom, because of some complication, it was deemed wise to terminate pregnancy in the early months and in whom any subsequent pregnancy would entail an equal or greater risk, 46 per cent.

3. As part of the procedure in extensive plastic operations on the cervix and pelvic floor accompanied by suspension of the uterus, 13 per cent.

In only one case was sterilization deliberately done as a procedure per se in the absence of pregnancy or other gynecologic operations and in that one the x-ray method was used. In all the others sterilization was performed in conjunction with other operative procedures, notably cesarean section and hysterotomy.

Such a policy could not have been followed had we not had a contraceptive clinic to which we could refer all patients presenting any condition rendering future pregnancies dangerous. The contraceptive advice there given has saved many women from operative sterilization. However, quite a number who have received instruction have, usually because of carelessness, become pregnant and they constitute quite a large percentage of the hysterotomy and sterilization cases.

If contraceptive advice has been given to a patient on a sufficient indication and she subsequently becomes pregnant, therapeutic abortion is usually advisable. As her failure to prevent this one pregnancy is presumptive evidence of future failure, she is given the option of surgical sterilization at the time of the operative termination of the pregnancy. It is our experience that the average clinic patient is less able or less willing to carry out contraceptive technique than is the average private patient, so that sterilizing operations are more often called for in the former than in the latter.

We shall now take up in detail each of the three groups of cases mentioned above:

1. *Sterilization at the Time of Cesarean Section.*—Seventy-one cases. The indications for sterilization in these cases were: (a) To prevent the risk of a subsequent section; (b) the presence of some condition rendering future pregnancy hazardous. I personally believe that a woman has the right to ask for sterilization at the time of a first cesarean section. If the section has been done because of pelvic abnormality or other conditions which simply prevent normal labor, and there is no condition present which would render subsequent pregnancy dangerous, she is

advised against sterilization; but, if after due consideration she and her husband still insist, her request would be acceded to. The advice against sterilization at a first section is, however, usually taken, for in the 23 cases in which such sterilization was done, definite indications against future pregnancies were present as follows: toxemia of various types 8; heart disease 8; tuberculosis 2; and one each of hydronephrosis, diabetes, mental defect, previous plastic operation in a para iii, and placenta previa in a para iii.

The choice of sterilization at the time of the second and third cesarean sections was much more freely exercised. It was done in 21 cases at the time of the second, and in 26 at the time of the third, section. In most of these patients there was present only a mechanical impediment to normal delivery and no pregnancy complications, so that sterilization was done simply to protect them against the risk of a future laparotomy.

The method of sterilization adopted in these cases of cesarean section varied; in some it was resection of the tube; in others subtotal hysterectomy. I believe that the latter is the procedure of choice if the patient will consent. It does not take longer to do than suture of the uterine wound and tubal resection, there is less blood loss, and the convalescence is easier and safer, for the organ in which infection is most likely to develop has been removed.

Provided the patient has not a "sentimental attachment" to the menstrual function, most of them will consent to this procedure if a little time is taken to explain to them that if they are to have no more pregnancies, the uterus is a useless organ, and that its removal will in no way unsex them. In my experience removal of the uterus does not tend toward an earlier menopause.

Sterilization at the Time of Abdominal Hysterotomy.—In the second group of cases, sterilization was done at the same time as a hysterotomy for the removal of an ovum before the period of viability. After fourteen weeks of gestation, we believe that the removal of the ovum is more safely accomplished by hysterotomy than by any method of dilatation or packing of the cervix. Vaginal hysterotomy is the method of choice in such cases if sterilization is not indicated, abdominal hysterotomy if it is indicated. Sterilization by resection of the tubes through the vaginal fornix can be done and is done by some operators at the same time as a vaginal hysterotomy. I personally do not like it as the blood loss from the incision of the cervix and the emptying of the uterus obscures the operative field and so very often renders the operation "sloppy."

In those cases beyond three and one-half months then, we regard the sterilization as an incident in the course of terminating the pregnancy by abdominal hysterotomy. But in 44 per cent of our cases of hysterotomy and sterilization, the pregnancy had not advanced beyond the second month. In these the pregnancy could have been easily and safely terminated by a simple dilatation and curettage. It might be said of them that the hysterotomy was an incident in the course of the operation for sterilization, the opening of the abdomen being necessary only for the latter procedure.

Little need be said regarding the third group of cases, those in which some gynecologic plastic operation had been carried out; a high amputation of the cervix, the repair of a large cystocele or rectocele, the repair of a long-standing third-degree tear, the repair of a bladder or rectal fistula, all of these render future childbearing undesirable. All of these women have borne children and in most of them the operative procedures are not done until they have acquired what they consider a sufficient family. If there is any doubt as to their capacity to use some contraceptive device, or if they are unwilling to do so, sterilization is indicated.

I am not going to discuss the technique of sterilization further than to say that in those cases in which hysterectomy is not done, I personally

prefer resection of the isthmic portion of the tube, covering the proximal end accurately with the peritoneal folds of the broad ligament. I may have had failures by this method but none have so far come to my notice. In our present hospital series, two patients became pregnant subsequent to a supposed sterilization, one by resection of the cornu and one by resection of the middle third of the tube. The following gives the percentages of the various procedures used by all members of the staff: (1) Ligation and resection of middle or isthmic portion, 54 per cent. (2) Resection of cornu, 21.4 per cent. (3) Pomeroy, 15 per cent. (4) Hysterectomy, 9.4 per cent. (5) Radiotherapy, one case.

From this brief summary, it is evident that in the Sloane Hospital sterilization is done in the majority of cases for conditions which render further childbearing hazardous to the mother. In only a small minority has it been done for eugenic reasons. The explanation for this is to be found in the comparatively small number of cases in the latter category which came under observation. When a definite eugenic indication is present, we believe sterilization is in order.

Finally, sterilization is called for in any case only because contraceptive methods are still imperfect. When a method, biologic or other, is evolved which is 100 per cent certain, and which does not emotionally upset either partner, sterilization will be unnecessary.

As surgical sterilization of the male is an easier and much less hazardous operation than that of the female, it might be thought that many devoted husbands would choose to have this done in order to save their wives. In my whole professional experience only one, and he a medical man, has made this choice.

LEGAL CONSIDERATIONS FOR THE PHYSICIAN*

WILLIAM J. MCWILLIAMS, NEW YORK, N. Y.
(*Attorney-at-Law*)

THE State of New York and nineteen other states in the United States have no statutes relating to human sterilization. The other twenty-eight states of the Union have laws providing for either compulsory or voluntary sterilization of mentally deficient or unfit persons, and pursuant to these laws at least 23,118 operations have been performed. Among these twenty-eight states there are four (Connecticut, Iowa, Kansas and Utah) that limit sterilization in private medical practice to cases where the performance of such operation is a "medical necessity."

An examination of all the varied relationships between the law and human sterilization is a subject too wide for this brief symposium. But the topic uppermost in the minds of most physicians may be stated in these terms: What is the civil and criminal liability, if any, of the operating physician in private practice in the United States who performs a vasectomy or salpingectomy? This limitation of the question makes possible a brief discussion of the major legal considerations important to the operating physician.

The first consideration in private practice in all cases is to obtain a consent to the operation from the patient. Judge Cardozo, now in the United States Supreme Court, stated the rule as to civil liability applying to all surgery, in these words: "A surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages . . . except in cases of emergency where the patient is unconscious. . . ."

Likewise, if the operation were performed without the patient's consent, it would constitute criminal assault, as well as civil.

A proper perspective in applying the law to sterilizations may be kept if familiar types of sterilization cases are first considered. The report made here this evening of work done at various hospitals shows that medical indications may require the removal of the uterus or the ovaries, or the severance of the fallopian tubes or of the vas deferens as an incident to the cure or prevention of disease. In such cases the usual routine hospital consent from the patient to operate is a complete shield to the operating physician against civil and criminal liability, even though the power to procreate has been destroyed, provided the operation is performed without negligence. Nobody is even mildly surprised at such operations or at the law. They are everyday medical experience.

But suppose the sterilization of either the man or woman is solely for eugenic purposes?

Recently a brilliant professional man disclosed to his physician in New York a family history of physical disorder and mental disease

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, November 24, 1936.

through two generations of ancestors and extending to his brothers and sisters, although the patient was apparently normal. The physician agreed with the patient that his offspring were likely to inherit the same disorder, and upon the patient's request performed a vasectomy. This was proper action on the physician's part. It is lawful in New York and probably in all states for a physician to perform a vasectomy or salpingectomy in private practice on a sane adult for the eugenic purpose of preventing procreation of children likely to be mentally defective or unfit. Possible exceptions to this general rule might arise (though it seems unlikely) in Connecticut, Utah, Kansas and Iowa, under future judicial interpretations of what is meant by "medical necessity" as contained in their special statutes limiting private sterilizations.

In the New York case just mentioned, the general criminal statute of the State covering maiming or mayhem does not apply, because the essential element of criminal intent to injure or maim is entirely lacking on the part of the physician. Further, there is no legal duty in the United States to have children, so the patient is not evading a civil obligation. The intent and purpose of the operating physician is the same as purpose approved in the famous case of Buck *vs.* Bell (274 U. S. 200) in which the Supreme Court of the United States held constitutional a Virginia statute compelling sterilization of feebleminded persons for eugenic purposes. This case of Buck *vs.* Bell definitely established the propriety of eugenic legislation. The constitutionality of laws providing for the sterilization of the unfit has been established in a number of states.

Now suppose the requested sterilization by vasectomy or salpingectomy is sought solely to remove danger of pregnancy of the wife? This type of case was considered by the Supreme Court of Minnesota in 1934 (255 North Western Reporter 620). A husband had himself vasectomized for the protection of his wife against another pregnancy. The operation was unsuccessful; the wife delivered a healthy baby. The husband sued the surgeon for damages. The surgeon, among other defenses, set up the novel plea that the performance of a sterilization operation on a healthy man was contrary to public policy and therefore illegal. The court found against the plaintiff on general grounds, but concerning this plea, the Court said, "Aside from the statutes in the few states that have prohibited it, we find no judicial or legislative announcement of public policy against the practice of sterilization. Certainly even in those states with statutory prohibition the exception of medical necessity would justify the physician in performing the operation here alleged. Plaintiff was married and presumably would remain married to his present wife, who had been competently advised of the danger of further pregnancy." (Rather than subjecting the wife to an operation for sterilization.) "It was entirely justifiable for them to take the simpler and less dangerous alternative and have the husband sterilized. . . . We therefore hold that under the circumstances of this case the contract to perform sterilization was not void as against public policy, nor was the performance of the operation illegal on that account."

It appears that there is no legal hindrance in private practice to performing a vasectomy for the purpose of preventing pregnancy in the patient's wife, except possibly in the four states previously men-

tioned, Connecticut, Iowa, Kansas and Utah, where it has not yet been decided by the courts whether such case would come within "medical necessity." These states will probably follow the Minnesota ruling above mentioned.

Suppose a woman, in order to remove the dread of unfit children or of dangerous pregnancy, goes to a physician and is sterilized without notifying her husband. In the few cases that have been considered, it is agreed that if the wife's consent is obtained, the consent of the husband is not necessary. If the husband's consent is not necessary for an operation on the wife, her consent should not be necessary for an operation on him. However, a prudent physician can avoid any question on this point by requiring both to join the consent, which should contain a plain statement of the nature and effect of the operation.

Suppose a patient under twenty-one years of age requests a salpingectomy or vasectomy for therapeutic or eugenic purposes; let us say, a boy or girl in the teen age. Such cases are not uncommon. If the purpose of the sterilization is therapeutic and incidental to the treatment of the patient's disorder, then the consent of at least one of the minor's parents or of the minor's guardian must be obtained before the operation is performed, and it would be advisable for the physician to obtain the consent of the minor where such minor is old enough to comprehend the operation.

However, if the proposed sterilization of a minor is for eugenic purposes, then the minor should be required to join with at least one of the parents, or the guardian, in the request and consent for the operation, and the physician should make very sure that the minor comprehends the nature and result of the operation.

If the minor happens to be married or emancipated from his or her parents, then such minor may be treated like an adult, although prudence on the physician's part would cause him to get consent of both parties to the marriage before operating on the minor spouse.

Finally, suppose the patient is a mentally defective person who has not been judicially declared incompetent. The physician in private practice who sterilizes a person of this class incurs a risk of civil, and possibly criminal, liability because the validity of the patient's consent may later be challenged. The physician must be prepared to show that such mentally defective patient had sufficient intelligence to understand that he or she could not beget children after the operation was performed, and requested the operation.

It is for the special benefit of mental defectives that many states have passed sterilization laws. The most highly regarded and widely used statute of this kind is in California. It provides that sterilization by vasectomy or salpingectomy is a prerequisite to the release of mentally defective persons who have been committed to state institutions, and it also provides for voluntary sterilization upon request of parent or guardian of a mentally defective minor or an incompetent adult. Vermont has another type of sterilization law providing for voluntary sterilization of adults or minors who are mentally defective, but the law contains no compulsory features. The Virginia statute, famous for being upheld by the U. S. Supreme Court in Buck *vs.* Bell, is entirely compulsory in its provisions and covers mentally defective persons in state institutions.

STERILIZATION AND EUGENICS*

FOSTER KENNEDY, M.D., F.R.S. (EDIN.), NEW YORK, N. Y.
(From the Department of Neurology, Cornell University Medical College)

IN THIS sphere of thought it is easy to be dogmatic, difficult to be right. For only fifty years has man been conscious of his own evolutionary development, and already many begin to realize that he will soon reach out toward conscious direction of that development. It is doubtful if as yet our brains are big enough, or our knowledge deep enough, to direct properly so gigantic an adventure. We would seem to have achieved our unique position of supremacy in the animal world by some inner power forbiding us, at any evolutionary crossroads, to take the path of specialization. We can see, but less well than an eagle—hear and jump, less well than a cat—swim less well than do fishes, and jump nimbly in the tree tops less well than our ancient collateral cousin, the ghostly Tarsius. If we really were to succeed in breeding for perfection as we do milch cows, we would be tempted to specialize, and to what end would we do so? What quality would we pick? Our figures show that of the children of a manic depressive, mated to a normal, one-third are manic depressive and of the children of a manic depressive mated to a manic depressive, two-thirds have the disease. One might say that this is prima facie evidence for sterilizing manic depressive individuals; but again one must look at the question from another point of view. We do not advance from century to century, from civilization to civilization, by reason of the mass of mediocre people, but by the ideas springing from the minds of the brilliant few. These brilliant few have often been cyclothymic persons who, afflicted often in their lives by periods of desperate depression, illuminate the world by flashing thoughts which come when energies and mental quickness are enormously increased during their periods of elation.

Sparta practiced infanticide more widely than other states for a military end. The Lacedaemonians were perfect, as a pack of wolves is perfect, but the glory of Grecian thought did not come out of Sparta. Julian Huxley has lately pointed out that it is improbable that human altruism will very greatly increase unless we entirely change our habits of procreation, setting aside individuals solely for this purpose, as do the insects, who have established thereby a rigid caste system. It is surely doubtful if man is ready to act on biologic truth when he is clearly content politically to live under a biologic lie. Germany at present has ordained that persons with schizophrenia and manic depressive insanity should be sterilized. When we consider that no man living knows anything of the pathology underlying these two conditions, it would seem premature and improper to lay unwitting hands upon them. However there is something to be said for the idea, not just of sterilization, but of castration of the criminal insane, in that eunuchs retain their intellect but lose initiative and emotionally are ideal seconds-in-command.

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, November 24, 1936.

Further, sterilization of the feebleminded is easy to advocate. We believe that 90 per cent of the cases of feeblemindedness show hereditary influence. In this matter we are undoubtedly breeding from the bottom, and we spend six times as much bringing up one mentally defective child as we do a normal child. Further, it would seem somehow proper that the group that pays for the support and upbringing of the offspring of defective individuals should have some say regarding their multiplication. However, there are five or six times as many cases of minds somehow disordered, outside institutions as in them. If we could devise a fitting standard for feeblemindedness, that is if we can catch the feebleminded and properly christen them—and there's the rub—I believe we can properly sterilize them.

In fine, sterilization of the feebleminded, if done largely and thoroughly, would, I believe, aid our civilization. Sterilization of manic depressive individuals might add to the human happiness of our immediate future, but almost certainly would slow up advancement of humanity in the long view. One day we will know more; then perhaps we can act firmly.

Men die, the ordered detail of each successive civilization dies, but from each wreck a thought, a theory, a conception of beauty, is saved, and serves as a torch to light the ways of men who seek again to build up the edifice of human society. Our knowledge is not quite sufficient to tell us what kind of mind will come from a particular kind of body, strong or ill. We can as yet only breed from the physical standpoint; and uniform physical perfection may contribute little, from generation to generation, to the advancement of thought or beauty, or the love of knowledge.

410 East Fifty-Seventh Street

STERILIZATION FROM THE STANDPOINT OF THE INTERNIST*

John Wyckhoff, M.D., New York, N. Y.

(From the Department of Medicine of the New York University Medical College)

THE interest of the internist in the subject of sterilization must be an interest which is broader than the effect of pregnancy upon chronic disease. It must include the effect of pregnancy on the patient who has chronic disease and that patient's environment, and also the effect of sterilization upon a woman of childbearing age who has no chronic disease. From the arrangement of this program I assume that others will discuss the various methods of the prevention of pregnancy. For these reasons I will limit myself as far as possible to discussing pregnancy as it affects the mother and child in chronic disease. I say chronic disease, for in acute disease it is difficult to think that permanent sterilization would ever be indicated. Such impressions as I shall give will be the impressions gathered by our staff at Bellevue.

I will speak first of pregnancy in the course of chronic diseases of the blood-forming organs. Numerous reports of successful pregnancy

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in patients suffering from chronic leucemia have appeared in the literature. One of Dr. Connery's patients discovered that she had leucemia while she was pregnant. A living child was born and as far as we could determine the patient lived the natural span of the disease. Another patient with chronic leucemia, probably the youngest in our series, passed a complete and successful pregnancy years after the diagnosis of leucemia had been made. The disease ran one of the longest courses we have ever seen.

During the course of pregnancy, anemia of several types and of varying degrees of severity is frequently seen. In almost all instances, this anemia may be relieved by diet or by iron or by a combination. Macrocytic hyperchromic anemia of the Addisonian type can be successfully treated. There are several reports showing increased life span in patients with pernicious anemia, when the treatment is adequate. I know of no reports that show that the course of the disease is shortened by the occurrence of pregnancy, or where the children born of such a mother were inferior.

In congenital hemophilia we have a different problem. A woman with the hemophilic taint in her blood bears children with great risk of transmitting to some of them a disease which at present can be treated only incompletely, and to all such children genes which may be transmitted to subsequent generations.

Hyperthyroid disease, being of frequent occurrence in women during the childbearing period and because of the effect of pregnancy in increasing the degree of hyperthyroidism, presents a definite problem. Patients with uncontrolled disease should not become pregnant. Many cases controlled either by Lugol's solution or operation complete pregnancies successful to both mother and child. Patients with hyperthyroidism who have true heart disease do very badly and should not become pregnant.

Diabetes per se is no contraindication to pregnancy. If a diabetic patient, however, should be unable to avoid repeated pregnancies, pregnancy would be contraindicated, as in the latter part of pregnancy the diabetes is likely to become very severe. Skipper recently discusses the question and says that each case should be judged individually. In making a decision he feels that such considerations as the economic condition of the patient, the number of children in the family already, and the mentality of the patient are important considerations because of the tendency of diabetes to occur in families. Some observers feel that childbearing in diabetic patients should be limited because of the possibility that in the future the child may develop diabetes. This obviously involves a discussion that would be endless, and I mention it because it is one of the points that occasionally is brought up.

There seems to be little in maladies of the digestive tract to indicate sterilization. These diseases of themselves are not hereditary. Peptic ulcer is not generally thought to constitute much of a hazard in pregnancy. Dr. Lockwood used to think that remission was the rule in pregnancy and Crohn says in his *Affections of the Stomach* that "conservative treatment of an ulcer during pregnancy is very promising." It is possible that vomiting of pregnancy might increase the ulcer risk but that would hardly be an indication for sterilization of the woman.

Renal disease and hypertension have to be considered from two aspects: (1) the influence *of* pregnancy *on* glomerulonephritis and

essential hypertension; (2) the influence *on* pregnancy *of* glomerulonephritis, essential hypertension and previous toxemia of pregnancy.

Active glomerulonephritis is a distinct contraindication to pregnancy. This is especially true when renal function is impaired. It is almost invariable that when a young woman with active glomerulonephritis becomes pregnant, in the first trimester there occurs an increase in proteinuria and hypertension. The mechanism is most likely a further degree of angiospasm on already sensitive arterioles. While there is no clear evidence to indicate that this type of exacerbation results in persistent further loss of renal function (as occurs in true inflammatory exacerbations of glomerulonephritis), there is great danger of permanent retinal damage with loss of vision consequent on the rise of blood pressure. On the other hand, glomerulonephritis in the latent state, i.e., proteinuria without hypertension or functional insufficiency, is no contraindication and such individuals are apparently no more susceptible to untoward occurrence than otherwise normal women.

Uncomplicated essential hypertension is rarely a contraindication to pregnancy. Most women with this condition go on to term or to the period of viability without the slightest difficulty. While such individuals are more prone to angiospasm in pregnancy and consequent increase in blood pressure than normal women, it most often occurs after the sixth month so that many can be carried to the period of viability if not to term. Moderate rises in blood pressure which may occur in these women tend to disappear rather promptly after delivery.

When essential hypertension is complicated by retinal hemorrhages and areas of degeneration, when before pregnancy the diastolic pressure is very high (120 mm. Hg or more) or when functional tests show distinct loss of kidney function, women should not become pregnant. Myocardial involvement due to coronary disease or previous cerebral accident, both of which might be influenced by a further rise in blood pressure, should also be considered contraindications.

In active glomerulonephritis, pregnancy rarely, if ever, goes to the period of viability. The frequent appearance of superimposed angiospasm in the first or second month leaves too long a period of morbidity. The rule is early miscarriage.

In uncomplicated essential hypertension in which the diastolic blood pressure is not above 100 mm. Hg, it is the rule for pregnancy to be entirely normal. When the diastolic blood pressure rises well above this, it is often necessary to induce labor shortly before term, since premature separation of the placenta may occur and result in a stillbirth.

Prediction as to the effect of a previous "toxemia" on subsequent pregnancies depends upon two observations: (1) the interval examination; (2) the number of previous "toxemias." If the patient makes a prompt recovery after delivery and over a period of one year there has been no recurrence of hypertension, she may be allowed a second pregnancy with little fear of serious recurrence. However, regardless of how prompt recovery was, the reappearance of even a mild grade of persistent hypertension makes the chance for recurrence great (about 60 per cent).

If the patient has had two successive "toxemias," it is the rule for recurrence to occur in subsequent pregnancies. While there are exceptions to this rule, there is no certain way in which such exceptions can be

predicted. The danger of permitting recurrent toxemia is evidenced by the latest available statistics (Herrick and Tillman) that about 50 per cent of these women develop persistent hypertension in the future.

The following quotation is from a report of the American Committee on Maternal Welfare, May, 1935: "Eclampsia and the forms of toxemia associated with it cause annually about 30 per cent of the approximately 15,000 maternal deaths in this country."

In rheumatoid arthritis, pregnancy is contraindicated not because of danger to the patient's life but because our present means of combating the disease consist almost wholly of conserving the patient's strength, and the increased burden of motherhood unavoidably adds to the patient's duties and responsibilities. It has been remarked by a number of writers that during pregnancy itself the patient with rheumatoid arthritis may appear to have a remission so that the impression has arisen that pregnancy may even be beneficial. However, it is my belief that in the long run this is not the case and that even those women who appear to improve during pregnancy are ultimately more likely to run an unfavorable course. On the other hand, I know two women with severe deforming arthritis who had successful pregnancies. They were both economically so situated as to care for themselves.

The heart diseases which occur during woman's fertile period are usually rheumatic; occasional cases of congenital heart disease may be a problem. The bacterial forms of heart disease, because of their acuteness, would hardly ever call for sterilization. Syphilitic heart disease might occasionally become a problem.

Cases of congenital heart disease usually do well if there is little or no diminution of the cardiac reserve before pregnancy. Those with cyanosis are likely to lose their babies. When there is marked diminution of cardiac reserve, pregnancy would be contraindicated. Such cases are rare. All that I have seen have done well.

Patients (inactive) with rheumatic heart disease with good reserve handle pregnancies rather well. I know of no evidence that pregnancy tends to be associated with increased occurrence of activity.

Patients inactive with greatly diminished reserve should not become pregnant. Such patients usually do not have intercourse but if they do, pregnancy should be prevented. Patients with active rheumatic heart disease nearly always have diminished cardiac reserve and while usually they live through a pregnancy they are liable to lose the child. Such patients should not become pregnant. However, many of these patients are active only temporarily and a number become inactive and develop sufficient reserve to go through a pregnancy. The question of advising sterilization in these cases, except the very obvious chronically incapacitated, places a great responsibility on the physician.

Last, an occasional woman may develop a syphilitic aortitis in her late thirties with signs of greatly diminished reserve, usually associated with signs of coronary thrombosis. Such cases do badly. Antisyphilitic treatment often is of no help. Their progress is rapid, the expectancy of life usually being under five years. Such patients should not become pregnant.

My own experience with tuberculosis is meager. It is well known that patients with active tuberculosis are made very much worse by pregnancy. It is also well known that many chronic active cases may cure and become arrested cases, but everyone who has had experience with

tuberculosis knows that there are chronic active cases with extensive lesions who, one may be sure, will never become inactive and in whom pregnancy should never be allowed. There is also the type of patient who has exacerbation of symptoms frequently with her menstrual period. Such cases, it is believed, have a much better chance of cure if an artificial menopause is brought about.

I have spoken of hemophilia, Graves' disease, active glomerulonephritis, previous toxemias of pregnancy, certain types of heart types, and certain types of tuberculosis, when occurring in women at the childbearing period, as being contraindications for pregnancy. In some of these, pregnancy could probably best be avoided by sterilization, but this should never be done in any case until all complicating factors are considered.

In avoiding the deleterious effects of pregnancy in certain forms of internal disease one must think of four things: the prevention of pregnancy by continence or contraceptives, or the prevention of pregnancy by sterilization, either temporary or permanent. The physician who advises permanent sterilization takes a serious responsibility. In general it would seem to me that the indications would be two: the first is where the woman carried an hereditary taint which she is certain to transmit, an example of which would be hemophilia; the second would be a form of chronic disease in which pregnancy or the additional burdens subsequent to childbearing will have serious deleterious effects upon either mother or child, or both, and in which there is practical certainty that the disease itself is either progressive or that it will never improve so as to safely allow a pregnancy. Examples of such indications would be in certain forms of the heart diseases and of tuberculosis.

DISCUSSION

DR. WILLIAM P. HEALY.—The eugenic side of the question seems to have, at least from the standpoint of the neuropsychiatrist, a very slender thread on which to hang. Certainly Dr. Kennedy takes little interest in it.

It is of interest that in the five years' work which Dr. Watson reported in an institution which handles so many abnormal maternity and gynecologic problems, in only 2 per cent did any question come up of the desirability of sterilization. That in itself must surely indicate that the question of sterilization, in obstetrics and gynecology, is one which we do not meet very frequently.

If we review what has been said here tonight, we can conclude that there are three factors which are closely related—contraception, therapeutic abortion, and sterilization. Contraception is very common and much sought after. Therapeutic abortion is willingly accepted. Sterilization is rarely desired. The question of sterilization is the important one and one that we will carry out in a relatively insignificant number of instances, as has been illustrated this evening by Dr. Watson.

We must bear in mind that there is a definite distinction between sterilization, so-called, induced by means of radiation therapy, and sterilization brought about surgically. With the use of radiation, you are very likely to bring about permanent castration with all the associated disturbing symptoms, whereas surgical sterilization does nothing but interfere with the possibility of conception. Therefore, one would hesitate to recommend that a young woman be sterilized by radiation methods, unless a surgical procedure, in itself, be too grave a procedure for that particular case.

Temporary sterilization with radiation therapy may be indicated, in certain conditions, largely of a neurotic type, in which we wish to observe whether certain mental

disturbances associated with the menstrual epoch disappear when the menstrual periods are diminished. If the symptoms no longer occur when there is amenorrhea, and on the return of the menstrual periods the symptoms recur, then one may go forward with permanent sterilization.

DR. HOWARD C. TAYLOR, JR.—The attitude of most people toward the subject of eugenic sterilization is dependent upon an emotional bias, quite outside the facts of the subject itself. We find perhaps three types of individuals. One group is almost ecstatically enthusiastic. These include the popular scientists, who believe that most of man's ills can be gradually eliminated by a careful selective program. They publish articles in a few scientific journals and in a good many Sunday newspapers. Second, there is a group which is equally vehement, in opposition. These include the sentimental liberals, who feel that the bearing of feebleminded children is one of the rights guaranteed the individual by the constitution. The third group is represented by those who make a sincere attempt to find the facts to arrive at some reasonable program.

This effort to find dependable facts carries some persons to the position taken by Dr. Kennedy tonight, for he feels that present data are too difficult to unravel, and that we are therefore not justified in any active steps. This is an attitude which I cannot believe to be sound. We must utilize the facts at present available and act on the conclusions arrived at. There is no way of avoiding some decision. To decide to allow the definitely feebleminded persons to continue to have children is as much a positive program as to decide to sterilize them. Although we may not be certain, we must go the way which is most probable. This, as a matter of fact, is the way man has always handled his social and political problems.

Let us consider what may be accomplished on the basis of the most dependable facts that we have at our command at the present time. Certain apparently carefully compiled statistics are to me impressive. For example, it has been calculated that one out of every ten of the feebleminded in this country have come of feebleminded parents (Punnett, Fisher). That means if all the obviously feebleminded are sterilized the number of feebleminded in the next generation will be reduced by 10 per cent. The question to be decided is whether it is worth while to sterilize or segregate, if you will, all the obviously feebleminded in order to bring about a reduction of the feebleminded in the next generation of only 10 per cent. Dr. Kennedy thinks that the benefits of such a program are too remote in the future to be worth aiming for; others will feel that the length of time required to produce results is the best reason for an immediate start.

Sterilization of the feebleminded has, however, an individual as well as a broad genetic aspect. One does not refuse to treat a case of pneumonia because further cases are not thereby prevented. A person with a fair chance of having feebleminded children must of course be considered also as an individual. If such persons appear to be incapable of taking care of potential children, whether these turn out to be normal or mentally deficient, then sterilization may have an immediate social indication quite aside from the remote genetic one.

Correspondence

Experiences With the Visscher-Bowman Pregnancy Test

To the Editor:

An article entitled, "The Chemical Determination of Pregnancy" was published about two years ago in which the authors, Drs. Visscher and Bowman, described a procedure which by chemical means determined the presence in the urine of the same substance which was found by biologic methods in the mouse or rabbit test.

We have done a total of 112 tests by this method, of which 94 were in known pregnancies and 18 in known nonpregnancies. Of the 94 pregnancies, 82 gave positive tests and 12 negative tests, or a percentage of error of 12.7 per cent. Of the 18 nonpregnancies, 7 gave positive tests and 11 negative tests, or a percentage of error of 38.8 per cent. In the total of 112 cases, there were 19 incorrect results, or a percentage of error of 16.9 per cent.

It would seem fair to conclude that this high percentage of error in a test of this type precludes the possibility of a practical value in the procedure.

SAMUEL B. SCHENCK, M.D., AND IRVING TRAN, M.D.

135 Eastern Parkway,
Brooklyn, N. Y.
June 21, 1937.

Roentgen Diagnosis of Triple Pregnancy

To the Editor:

In the August, 1936, issue of the JOURNAL I reviewed the literature on triple pregnancy diagnosed by x-ray, giving a short summary of the nine cases reported and adding a tenth case from my own practice. At that time I overlooked one case reported by Greenhill in *Medical Clinics of North America*, September, 1923, and 2 cases reported by Weil in *Gynécologie et Obstétrique* for October, 1935. E. W. Titus also reported one case in the April, 1937, issue of the JOURNAL, thus bringing the total number of cases reported to 14. I would like to add the fifteenth case, a patient recently delivered on the Obstetrical Service of the University Hospital, University of Maryland School of Medicine.

H. S., colored, aged fifteen years, single, primipara. The family history is interesting in that her maternal grandmother had 2 sets of twins and one maternal great grandmother had one set of twins. The patient's past history was negative. Her last menstrual period was Aug. 20, 1936, making her estimated date of confinement May 27, 1937. She was first seen in the Out-Patient Department on Nov. 13, 1936 at which time she was thought to be about sixteen weeks pregnant. Kolmer 4-4 was repeated with the same result, weight 112½ pounds, pelvic measurements were slightly less than normal but not enough to cause any concern as we deliver a large number of small colored girls in the clinic without difficulty.

Her prenatal course was normal except for an elevation of blood pressure to 132/78 on December 14 and 132/98 on March 29. She was rather uncooperative about reporting for antisyphilitic treatment and received six treatments only at irregular intervals. The patient was examined on March 29 and because of the marked

protuberance of her abdomen the chief-of-clinic asked that special attention be paid to any disproportion. At this time a diagnosis of twins was made and an x-ray examination requested to confirm or disprove the diagnosis. The x-ray plates showed distinctly 3 fetal heads and spines, confirming the diagnosis of multiple pregnancy but showing triplets instead of twins. She had gained 22 pounds in four and one-half months.

On April 1 labor began spontaneously and proceeded so rapidly that at the end of two hours the cervix was completely dilated and the head of the first baby low in the pelvis. The patient was prepared for delivery and after a right paramedian episiotomy the head, which was lying in R.O.T. position, was manually rotated to an R.O.A. and a living female child weighing 3 pounds 11½ ounces was delivered by low forceps. The second head was easily pushed down into the pelvis and a living male child weighing 3 pounds 9½ ounces was delivered by mid-forceps, position was L.O.A. The head of the third child was likewise pushed into the pelvis in R.O.T. position. Following manual rotation to an R.O.A. position a living male child weighing 3 pounds 14¾ ounces was delivered by mid-forceps.

The third stage was uneventful. Inspection of the placenta indicated that the male children were identical twins and the female a separate ovum impregnation. Inspection of the cervix revealed a deep laceration on the right that required six sutures. The episiotomy was repaired in the routine manner. Mother and babies were in good condition one hour postpartum.

The puerperium was characterized by an elevation of temperature, the highest being 102° on the eighth day, and foul lochia. The pulse, however, was not markedly elevated at any time nor was the patient ever very ill. The temperature fell by lysis and on the seventeenth day she was fever free. She was discharged on the twentieth day in good condition.

The babies were given breast milk by gavage for the first few days and then a formula of evaporated milk and dextri-maltose. The latter they were able to take from a bottle. The babies all did well. Baby 1, a girl, discharged on May 8 had gained 1 pound 9 ounces. Baby 2, a boy, discharged on May 12 had gained 1 pound 10½ ounces. Baby 3, a boy, was discharged on May 8 having gained 1 pound 5½ ounces. All three were in a satisfactory condition and are still living and gaining at this date.

MARGARET B. BALLARD, M.D.

104 West Madison Street,
Baltimore, Md.
June 29, 1937.

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF DECEMBER 8, 1936.

The following papers were presented:

A Study of the End-Results of the Treatment of Amenorrhea and Sterility by Radiation of 128 Married Women Over a Period of Ten Years. Dr. Ira I. Kaplan. (By invitation.) (For original article, see page 420.)

Early Diagnosis of Carcinoma of the Cervix. Dr. Walter Schiller. (By invitation.)

MEETING OF JANUARY 12, 1937

The following papers were presented:

Pyeloureteritis in Pregnancy: Etiology, Acute Phase, and Treatment. Dr. Herbert F. Traut. (For original article, see page 392.)

End-Results of Urinary Tract Infections Associated With Pregnancy. Dr. E. Granville Crabtree. (For original article, see page 405.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF JANUARY 7, 1937

The following paper was presented:

Surgical Complications of Pregnancy. Dr. S. A. Cosgrove. (For original article, see page 469.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 23, 1936

The following paper was presented by invitation:

Pathology of the Cervix. Dr. Walter Schiller. (For original article, see page 430.)

Episacroiliac Lipoma. Dr. Emil Ries. (For original article, see page 490.)

MEETING OF NOVEMBER 20, 1936

The following papers and case report were presented:

Splenomegaly in Pregnancy. Dr. W. B. Serbin. (For original article, see page 486.)

The Effect of the Ovarian Hormones on the Human (Nonpuerperal) Uterus. Drs. Leon Krohn, J. E. Lackner and S. Soskin. (For original article, see page 379.)

Carcinoma of the Cervix During Pregnancy. Dr. W. C. Danforth. (For original article, see page 365.)

MEETING OF JANUARY 15, 1937

The following papers were presented: **Experimental and Clinical Therapy of Vulvovaginal Mycoses.** Dr. H. C. Hesseltine. (For original article, see page 439.)

The Mortality and Complications of 3,129 Supravaginal Hysteromyomectomies. Dr. H. E. Schmitz. (For original article, see page 480.)

The Oral Administration of Paraldehyde for Relief of Pain During Labor. Drs. Edwin J. DeCosta and Ralph A. Reis. (For original article, see page 448.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 3, 1936

The following papers were presented:

Medical Aspects of Heart Disease in Pregnancy. Dr. Arthur E. Lamb. (For original article, see page 456.)

Management of the Dystocia Caused by Occiput Posterior Positions. Dr. J. Thornton Wallace.

MEETING OF DECEMBER 4, 1936

The following case reports and papers were presented:

Ectopic Gestation Following Pomeroy Sterilization. Dr. Martin H. Lutz (By invitation). (For original article, see page 497.)

Angiomatosis Retinae (von Hippel's Disease, Lindau's Disease) Complicated by Pregnancy. Dr. Mervyn V. Armstrong. (For original article, see page 494.)

Management of Pregnancy and Parturitional Hemorrhage. Dr. S. A. Cosgrove. (Published in *The Southern Medical Journal.*)

NEW YORK ACADEMY OF MEDICINE, SECTION ON OBSTETRICS AND GYNECOLOGY

MEETING OF NOVEMBER 24, 1936

Symposium on Sterility

Eugenic Sterilization in Europe. Marie E. Kopp, Ph.D. (For original article, see page 499.)

Sterilization From the Standpoint of the Internist. John Wyckoff, M.D. (For original article, see page 520.)

Sterilization and Eugenics. Foster Kennedy, M.D. (For original article, see page 519.)

Sterilization From the Point of View of the Obstetrician and Gynecologist. B. P. Watson, M.D. (For original article, see page 512.)

Operative Methods of Sterilization in the Female. Eliot Bishop, M.D. (For original article, see page 505.)

Sterilization by Irradiation. Ira Kaplan, M.D. (For original article, see page 507.)

Legal Considerations for the Physician. W. J. McWilliams, Attorney-at-Law. (For original article, see page 516.)

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 24, 1936

The following papers and discussions were presented:

The Function of the Levator Ani Muscle. Dr. James R. Costello.

Breech Presentation: A Critical Analysis of 285 Cases of External Version, Cesarean, the Anesthesia Used, Incidence of Forceps, Use of X-Ray Diagnosis. Drs. W. C. Danforth and C. E. Galloway. (The original article will appear in a later issue.)

MEETING OF DECEMBER 4, 1936

The following papers and discussions were presented:

Endometriosis. Dr. J. Keith Cromer.

Medical Notes from the Soviet. Dr. Richard L. Silvester.

Functional Dysmenorrhea, an Endocrine Problem and Its Treatment. Dr. J. Kotz. (For original article, see page 38, July, 1937, issue.)

Department of Reviews and Abstracts

Conducted by Hugo Ehrenfest, M.D.

Collective Review

MENSTRUATION AND ITS DISORDERS

A Critical Review of the Literature from 1933 to 1936 Inclusive

Hugo Ehrenfest, M.D., St. Louis, Mo.

WITHIN the last few years extensive experimental and clinical studies have yielded much interesting and valuable information in regard to the control exerted by the anterior lobe of the pituitary (A.P.) gland on the process of ovulation, in regard to time and causative relations between ovulation and the menstrual flow, the rôle played by endocrine factors in the various disorders of the menstrual function, and finally concerning the efficacy of certain organ extracts in the treatment of such disorders.

A critical review of this voluminous literature, in part not readily accessible to the gynecologist, seems desirable for the purpose of familiarizing him with this literature and thus enabling him to differentiate between actually established facts and many still unproved theories and opinions. The multiplicity of these investigations and reports inevitably has resulted in some confusion of views concerning the factor or factors responsible for the many possible anomalies of the menstrual function and their therapeutic relief.

Deliberately, this survey has been limited to contributions published between the beginning of 1933 and the end of 1936. Even so and in spite of almost complete elimination of merely experimental endocrine studies on animals, it became necessary to quote in the text 394 references cited in the appended bibliography. This can not be surprising in the face of Mengert's[1] assertion that the volume *Sex and Internal Secretion,* edited by Allen, required consideration of 2474 individual papers (monographs and books being excluded) published in 335 different scientific journals. Reviewing the literature published within but two years on the "Interrelationship of Anterior Hypophysis and Ovary," Fluhmann[2] carefully selected "only information of possible interest to obstetricians and gynecologists," and nevertheless was compelled to quote 246 papers—he states: "Study of this literature leaves one aghast at the extent and complexity of the problem."

Almost the same statement could be made in regard to the literature of the past four years dealing with the problems of menstruation. At the moment it is not even possible to define the word "menstruation" as presently employed in the literature.

I. DEFINITION OF "MENSTRUATION"

In the attempt to bring some order into prevailing confusion and inaccuracies of terminology, we shall here use the term "menstruation" to designate the physiologic process which between menarche and menopause periodically prepares woman for the implantation of a fertilized ovum. "Menstrual flow" is the uterine hemorrhage associated with the elimination of the pregravid decidua in case the anticipated impregnation has not taken place.

Outside of these true menstrual flows there can occur, spontaneous or artificially produced, sanguineous discharges from the uterus which must be termed "menstruation-like" flows when occurring in fairly regular intervals. We shall say more about them later.

The old and time-honored conception of "menstruation" as a manifestation of a merely local, uterine process had to be discarded after it had been established that there occur cyclic changes not only in the ovaries but also in the endometrium (Hitschmann and Adler), and after it had become clear that these periodic structural changes in both organs are intimately related to simultaneous systemic changes of the entire organic structure of woman, changes which definitely modify all metabolic activity and even the otherwise almost constant chemic constitution of body fluids. Thus was evolved the generally accepted view of the intimate and purposeful connection between menstruation and pregnancy. An important and essential part of this view necessarily is the conception that there can be no menstrual function without ovulation.

Corner, Hartman, Allen among many others have shown that a periodic, menstruation-like flow without preceding ovulation is a fairly frequent occurrence in normal monkeys, especially during the summer months, and an occasional occurrence also in woman. Anatomists, embryologists, and other scientific investigators thus began to speak of "anovulatory menstruation." Such usage of the term menstruation undeniably is objectionable from the viewpoint of the obstetrician, since it runs counter to the indisputable fact that a true menstrual flow depends upon the formation of a corpus luteum. R. Schroeder (in Veit-Stoeckel's *Handbuch der Gynaekologie*) insists that a menstrual flow definitely represents the uterine hemorrhage which terminates a complete ovulatory cycle and originates from an endometrium in its typical secretory phase of development. All other periodic hemorrhages can be designated only as "menstruation-like."[3] With considerable emphasis similar views have been expressed by Robert Meyer, Muehlbock,[4] Zondek,[5] Shaw,[6] and many others. Shaw refers with slight irony to Novak's "still unproved" contention that such anovulatory flows in women are more frequent than generally assumed. The possibility of such an occurrence now has been established, but it seems entirely unjustified, in my opinion, to assign to this phenomenon any particular importance in the problem of sterility. Such flows without preceding ovulation do occur in some monkeys occasionally, but there certainly is no proof that they continue in women for periods so long as to account for a sterility persisting for years. Even women who actually menstruate only two or three times a year are not necessarily or often sterile.

Scientifically the menstrual function has been recognized as a local and general systemic, periodic preparation for impregnation. This great and valuable advance in our information concerning the biology

of woman will be vitiated by wider use of the term "menstruation" for a menstruation-like uterine flow which is not dependent on ovulation. We are unwilling to agree with Emil Novak's contention that these flows might as well be called menstruations, because this term is in general use in referring to periodical flows in mature women. It seems ludicrous to see, more recently, authors writing of "restoration of menstruation" in castrated women, simply because administration of certain organ extracts was followed by a bloody vaginal discharge. Such a flow, as a rule, is procured only for one time and thus is void even of the characteristic periodicity. Gynecologists will, or should, not accept Allen's[7] proposal to term as menstruation any flow due to disintegration of the endometrium under hormonal influence, whether natural or artificially produced. Much confusion and misleading ideas would be avoided if, especially in clinical reports, authors would clearly differentiate between menstrual and menstruation-like flows.

II. OVULATION

The following vivid description of ovarian activity has been given by Hartman:[8] The ovary is never resting. Its cellular turnover is probably the largest of any other organ in the female body except possibly the skin. It seems that about 25,000 eggs through degeneration of primordial follicles are sacrificed within the period of a menstrual cycle, so that one choice egg may survive and mature, and by a fortuitous set of circumstances develop into a baby. The many thousands of follicles which degenerate, nevertheless, prove useful, because they give off internal secretions that minister to certain vegetative functions of the female body: first, to keep healthy and active the female organs for possible pregnancy and lactation; second, to preserve the secondary sex characteristics; and third, to provide the proper hormone balance necessary for the feeling of well being needed for the full enjoyment of life. During the middle of the cycle the ovary seems more active, because among the many degenerating follicles, a single one "gets by" and develops to maturity. . . In women like in many other animals, ovulation is a spontaneous process regulated by the function of the anterior pituitary gland.

It has been known for a long time that endocrine activity of the ovaries, even before the appearance of the first menstrual flow, is responsible for the gradual change of the infantile into the mature type of uterus and for the development of the secondary sex characteristics. It has been assumed, and with more recent investigations the fact has been established, that the appearance of the first and of all subsequent true menstrual hemorrhages depends on a complete ovulation cycle, beginning with the enlargement of a primordial follicle and ending in the formation of a corpus luteum, which represents a specific, periodically new-formed endocrine gland with its own specific hormone or hormones.

Zondek, as the first, established the control of the anterior lobe of the hypophysis over the complete ovulatory cycle. There is considerable supporting evidence for the assumption that specific activity of the anterior pituitary does not begin until the thymus gland is involuted. Continuing their researches along these lines, Fleischmann and Goldhammer[9] recently reported that they found in the urine of 9 out of 20 infants, between two and eight years of age, a substance which definitely inhibits the estrus of white mice. In view of certain analogies

with results of previous experiments, they feel justified in concluding that this substance represents thymus hormone. We shall have opportunity later to speak of the rôle played by the active hypophysis also in the artificial production of menstruation-like flows with the administration of certain organ extracts. These latter experiments together with new, relatively simple methods of obtaining endometrial tissue for microscopic study (to be described later) at any phase of the cycle, have greatly advanced our information concerning the definite relations between ovarian and endometrial changes.

Most writers still adhere to the four endometrial phases as first described by Hitschmann and Adler, but Allen[7] suggests the omission of their "interval stage." He substitutes for it his Stage I: a period of postmenstrual repair and growth of the endometrium—the follicular phase under stimulation of the estrogenic factor. In his Stage II the endometrium changes in two possible ways: (a) *If ovulation occurs,* the glands are transformed with change in the nature of their secretions under stimulation of progestin from the corpus luteum (with some estrogen substance still present in the woman), but he adds: "This second stage is not necessary for menstruation." (b) *If ovulation fails to occur,* there follows a phase characterized by sustained but waning hyperplastic endometrium under the influence of diminishing concentration of estrogenic hormone. "This type of cycle is normal in monkeys out of breeding season and is an occasional occurrence in adult women and may be a frequent occurrence near the times of puberty and the menopause." Allen's Stage III is that of the menstrual hemorrhage which physiologically represents the terminal event of the cycle.

However interesting or important such a classification of endometrial changes may be to the scientific investigator, its incidental assertion, that these two kinds of flows, though absolutely different in their biologic causation nevertheless are identical, seems unacceptable to the clinician. In the present endeavor to gain a clearer understanding in the complex problem of "functional uterine hemorrhages," the gynecologist will do well to limit the term "menstruation" strictly to the flow resulting from the disintegration of an endometrium variously designated as predecidual, pregravid, progestational, clearly expressing structural preparation for pregnancy. Allen,[7] Corner,[10] Hisaw, Kaufmann,[11-13] Loeser,[14] Zondek,[5] and many others, experimentally on animals and more lately on castrated women with the administrations of certain endocrine preparations, have conclusively shown that this phase of the endometrium is due solely to the specific hormone evolved by the corpus luteum.

Before entering into a discussion of clinical differentiation between true menstrual and pseudomenstrual or so-called functional uterine hemorrhages, it will be necessary to deal with newer information concerning the time of ovulation.

III. THE TIME OF OVULATION

Interest in the time of ovulation was greatly stimulated by the wider spread, under sanction of the Catholic church, of the use of the safe period as available means for the prevention of impregnation. From this special viewpoint this question is thoroughly and most interestingly discussed in a small volume by Carl G. Hartman.[8]

By way of introduction, we may refer to the fact that Araya,[15] in contradiction of generally held views, from observations made on 464

patients, concludes that menstruation and ovulation are two entirely independent processes. He[16] even denies the necessity of a pregravid endometrium for nidation of a fertilized ovum. In a recent third paper,[17] he summarizes his views to the effect that obviously the ideas of Knaus and Ogino of the existence of a safe period are untenable. Similar views have been expressed by Borras.[18] Kreis[19] defends his idea of an independence of endometrial changes from the ovary.

Older efforts of determining ovulation time by graphing waves in various physiologic functions (Jacobi), of "well-being" (Dickinson), of sex desire (Katharine B. Davis, Tinklepaugh, Stopes, Havelock Ellis, etc.), by studying assumed "isolated coitus," wedding dates or results of artificial insemination are, as Hartman justly asserts, scientifically unacceptable. At least more definite are local symptoms and among them especially the "Mittelschmerz" which not so rarely is accompanied by a light "intermenstrual bleeding." Such recorded observations of Mittelschmerz, with or without bleeding, falling somewhere between the fourteenth and nineteenth days of the cycle (counted from the first day of the flow), in general would seem to support the contention of Knaus and Ogino but do not permit any definite deductions as to ovulation time. In none of these studies, writes Hartman, was the condition of the ovaries checked by palpation or abdominal inspection. We must interpolate here reference to a paper quite recently published. Wharton and Henriksen[20] discuss in detail the entire "*Mittelschmerz*" problem and then present a clinical study of 61 cases of intermenstrual pain, in 30 of which laparotomies were performed for various reasons. Data obtained by them indicate that the Mittelschmerz is synchronous with rupture of the mature graafian follicle.

Exact palpation of the ovaries, of the gradual enlargement of the follicle and formation of the corpus luteum is possible only in monkeys, and such palpatory findings, repeatedly controlled by laparotomy, have in every instance shown that at the time of the intermenstrual bleeding a large follicle or a fresh corpus luteum was present (Hartman). Some data concerning systematic palpation of ovaries in human females have been supplied by Dickinson and others.

Observations of peaks in estrogenic hormone levels in the blood in the midinterval (Frank,[21] Emge,[22] Fluhmann,[23] and others) presumably correspond to the ovulation time and are ascribed to the introduction of larger amounts of follicular hormones with full ripening and rupture of the mature follicle. Kurzrok, Kirkman, and Creelman[24] presented a paper in which they claimed that the time of human ovulation is also manifested by the sudden appearance of prolan A in the urine. In the discussion of this paper, Frank stated that he is willing to accept this observation as proving a cyclically increased activity of the anterior pituitary but not as establishing ovulation time. Analyzing the local and general symptoms of ovulation, Simonnet and Brandwein[25] stress the observation that the intermenstrual pain is usually observed between the twelfth and sixteenth days of the cycle, the increase of follicular hormone, both in blood and urine, between the eleventh and fifteenth, so that seemingly the maximum of folliculin elimination coincides with follicle rupture.

It seems opportune to mention here a few contributions which refer to the fallacy or, more precisely expressed, the impossibility of estimating the time elapsed since follicular rupture by the size or appearance

of the corpus luteum. Emil Novak states that in the study of many thousands of ovaries he has never seen the earliest stage of a corpus, indicative of immediately preceding rupture. "In later stages nobody would venture an estimate of the exact time at which ovulation had occurred." It is Papanicolaou's experience that the exact age of the corpus luteum in women could not be recognized even from detailed histologic study. Hartman, himself, admits only his ability to differentiate between a very young and very old corpus luteum, and asserts that in monkey and human female an estimate of the age of a corpus is bound to lead to crass errors. However, systematic inspection of ovaries of women and monkeys, in general, proves that in the vast majority of instances ovulation falls close to days fourteen to sixteen of the cycle, that is, takes place when the endometrium changes from the late proliferative into the early secretory phase. All this, Hartman admits, does not exclude the possibility that exceptionally ovulation might occur at any other time which, as we should remember, is contrary to Ogino's most emphatic assertion that ovulation takes place only between the eleventh and sixteenth days and to the claim of Knaus that the mature follicle ruptures exactly fourteen days before the ensuing menstrual flow.

Knaus[26] developed his method of determining ovulation time in woman on the basis of Reynold's observation that the uterine muscular tonus is increased under estrogen influence and relaxes with the formation of the corpus luteum. In this latter state, Knaus found that the hormone of the posterior pituitary lobe (pituitrin) proves ineffective on the uterine muscle. He thus arrived at the conclusion that the endocrine activity of the corpus luteum of menstruation always lasts exactly fourteen days. This claim has never been confirmed by any other investigator. Hermstein,[27] studying 30 women by means of the Knaus method (small rubber balloon in uterine cavity connected with a manometer), found at least a few exceptions. Morgan, Moir, Tachezy[28] and others disagree with Knaus but some of these discrepancies, as pointed out by Hartman, might possibly be explained by occasional anovulatory (menstruation-like) flows, whose occurrence also Knaus[29] admits. Knaus thinks that the nature of such a flow, i.e., the absence of a corpus luteum, can be recognized by a positive uterine response to pituitrin within ten days of the next expected flow. A clear and critical analysis of the literature dealing with ovulation time, particularly in its relation to the problem of the safe period, will be found in a paper by Emge.[22] Shaw[6] thinks that a fairly free interval bleeding might be wrongly interpreted as an anovulatory "menstrual" flow, but that, on the other hand, a true menstrual flow at an irregular time may be due to the premature rupture of an almost mature follicle as a result of coitus, a phenomenon which is almost the rule in certain animals.

No control experiments are as yet available in regard to the recent observation of Burr, Hill, and Allen[30] that in rabbits the exact moment of the rupture of each follicle can be discovered by a registrable change in electric potentials.

To obviate repetition we shall speak later of attempts to influence ovulation time by the administration of certain hormones.

Concluding this consideration of chronologic relation of ovulation to the appearance of the menstrual flow, we can say that investigations

carried out in various ways practically agree in the finding that in the overwhelming majority of normally menstruating women ovulation occurs near the middle of the interval.

IV. MENSTRUAL FLOWS

The determination that a given uterine hemorrhage represents a true menstrual flow depends on the proof that it originates from an endometrium in its characteristic secretory phase. As already mentioned, it is not any longer necessary to curet a patient (in a hospital, under anesthesia) for this purpose. Smaller pieces of endometrium, sufficient for microscopic study, are now obtained in the office, without noteworthy discomfort, by various means at any phase of the cycle. Some gynecologists use a very small (monkey) curet (see Sturgis and Meigs[31]). Burch[32] designed a suction cannula. A similar cannula is employed by Novak[33] which more recently has been modified by Tamis.[34] It may be stated in this connection that these methods are valuable not only for the purpose of scientific investigations but also for clinical purposes, as, e.g., in determining the specific endocrine functional anomaly responsible for various disorders of the menstrual flow. It also must be emphasized that these methods should never replace a thorough curettage in any case in which a uterine malignancy is suspected. For reliable diagnosis complete removal of the entire endometrium is essential. Another shortcoming of studies of small pieces of endometrium is suggested by the claim of Bartelmetz[35] that there is a definite variability in the histologic picture of the menstruating endometrium in various regions of the uterine cavity. This observation harmonizes with studies made by Markee[36] on pieces of endometrium implanted into the eyes of six monkeys. However, Robert Meyer[37] is unwilling to accept the claim of Bartelmetz that at a given moment the various parts of the endometrium will exhibit different degrees, either of pregravid change or of epithelial exfoliation.

Direct observations of cyclic changes in endometriomas have been reported. In a patient of Chydenius[38] a large vaginal metastasis had formed from a primary ovarian endometrioma. Repeated removal of small pieces taken from the metastasis enabled him to ascertain that the endometrial tissue of the growth underwent the typical cyclical changes. Engelhard[39] recorded regular discharge of blood at every menstrual period from a pea-sized metastatic endometrioma located in a small labium.

Before entering into a discussion of endometrial structural changes culminating in the menstrual flow, it will be necessary to refer to newer information in regard to the *function of the anterior lobe of the hypophysis*.

Mention already has been made of an analysis by Fluhmann,[2] published in 1933, of 246 papers on the relation of the hypophysis to the ovaries appearing within the two preceding years. It must be obvious that it would be impossible to review here the literature on this same subject published since then. Therefore, we shall limit ourselves to brief references of those contributions which seem significant in regard to present views on normal and disordered menstrual function and to the treatment of the latter with certain organ extracts.

Experimental studies of the last decade, states Evans,[40] have now given adequate grounds for belief in the existence of at least five separate internal secretions of the anterior pituitary lobe. However, we are here solely concerned with the gonadotropic hormones of women discovered almost simultaneously by Zondek and Aschheim, and P. E. Smith. The gonad-stimulating effect of the anterior pituitary on the ovary is definitely established to be due to two hormones: one, the follicle-stimulating hormone which causes the enlargement and development of the primordial to the mature graafian follicle, the other, the luteinizing hormone which is more directly concerned with the formation of the corpus luteum. Both the ripe follicle and the corpus luteum in turn become sources of other specific hormones. Moricard[41] recently reported the effect of removal of an adenomatous hypophysis in a normally menstruating woman. She became amenorrheic and two years later the internal and external genitalia had become markedly atrophic. Her urine then still showed 10 R.U. of folliculin per liter, but, as pointed out by Moricard, this does not imply continued ovarian activity, because this same phenomenon is commonly observed also in castrated women.

In early pregnancy there appear promptly and regularly (Aschheim-Zondek pregnancy test) in the urine substances which, at first and up to recently, were considered to represent typical gonadotropic hormones produced, under the influence of pregnancy, in enormous quantities by the anterior lobe of the hypophysis. More lately two important facts have been revealed: the substances readily extracted from the urine of pregnant women (or mares) are not produced in the pituitary gland and are biologically only similar to but not identical with gonadotropic hormone extracts made from pituitary gland tissue. For evident reasons the latter are obtainable only in limited amounts for experimental purposes, as a rule prepared by the experimenters in their own laboratories. The so-called anterior pituitary preparations on the market, more correctly termed anterior pituitary-like (A.P.L.) substances, for clinical use are manufactured in larger quantities from the urine of pregnant women and more recently extracted from placentas (Collip's emmenin).

In experiments on hypophysectomized animals, the gonadotropic substances of pregnancy urine become effective on the ovaries only in combination with an extract made directly from the anterior pituitary lobe, which Evans for this reason designates as an essential "synergist." Fevold and Hisaw have suggested that this synergist is identical with the follicle-stimulating hormone of the anterior pituitary gland.

Philipp and Huber[42] have recently summarized all available evidence, to a great part the result of Philipp's own studies, which very strongly suggests that the gonadotropic substances of pregnancy urine really are produced by the placenta. More will be said later on this question.

After this digression we may return to the rôle played by the anterior lobe in the processes of ovulation and menstruation. It would seem, states Allen,[7] that the follicle-stimulating hormone of the anterior pituitary (prolan A) induces the growth of follicles and secretion of the follicular hormone, which latter reacts on the anterior pituitary to induce secretion of the luteinizing factor (prolan B). The latter aids in the development of corpora lutea which produce the hormone progestin. The follicular hormone (and possibly also progestin) may temporarily act on the anterior pituitary, depressing its secretion of follicle-stimu-

lating hormone. Approximately in this manner the cyclicity of ovarian and endometrial function is explained on the basis of a cyclicity of anterior pituitary activity.

Only slightly different is Hartman's[8] description of hypophysis-ovary interrelations. Prolan A stimulates the growth of the follicle, the latter secretes more estrogenic hormone, which affects the uterus, endometrium and vaginal mucosa. Continued output of prolan A combined with prolan B brings about ovulation and formation of a corpus luteum. This starts the secretory phase in the endometrium. Sloughing of the epithelium brings the flow which ends the cycle. Still another slight variation of views can be noticed in the report of experiments made by Brindeau, H. Hinglais, and M. Hinglais.[43] They claim that prolan A (Zondek) consists of two components, one stimulating follicle maturation and another sensitizing the follicle to the luteinizing properties of prolan B.

There is, or at least was up to recently, some dissension of opinions concerning the rôle played by the mature and unfertilized ovum both in the formation of the corpus luteum and in the development of the pregravid phase of the endometrium.

Among recent writers, we find Schoeller[43] still adhering to Robert Meyer's view that the transition of the proliferative into the secretory stage of the endometrium occurs under the luteinizing effect of the mature ovum. Westman,[44] on the other hand, feels that most painstakingly performed experimental studies seemingly have supplied convincing proof that the luteinization process is not dependent upon any hormonal influence exerted by the not fertilized ovum. The most important work in this respect has been done by Zondek who in a recent paper[5] remarks that the idea of a supremacy of the egg cell has been given up ever since he had definitely demonstrated that corpus luteum formation is solely controlled by anterior pituitary function.[45]

Prevailing disagreement concerning the factor or factors which cause the endometrial bleeding at menstruation time, in the main, is due to the insistence on the part of some scientific investigators that true ovulatory menstrual flows and menstruation-like anovulatory flows are identical phenomena. Common to both is the fact that they probably are caused by quantitative changes in certain sexual hormones; they differ, however, in regard to the structural condition of the bleeding endometrium. With but few exceptions modern writers explain the hemorrhage on the basis of increased or decreased output of follicle or corpus luteum hormones, or ascribe it to a disturbed equilibrium thereby caused between them.

As already pointed out, the idea of a supremacy of the unfertilized ovum is untenable. The few writers, previously quoted, who believe in an endometrial cycle quite independent from the ovarian cycle, stand rather isolated. Thus, we can well limit ourselves here to a discussion of views which explain the periodic uterine flow as due to cyclic alterations of folliculin and progestin output.

Engle and his coworkers[46] agree that the problem of the actual cause of "menstruation" (this ambiguous term is used by them) is not yet solved. Three theories are current:

I. It is due to cessation of corpus luteum activity, that is, to the withdrawal of progestin, which represents the more generally accepted theory, "which is applicable only to the complete ovulatory cycle."

II. It is due to a lowering of the estrin level. This theory is evolved from the finding that in monkeys there exists a nonovulatory cycle (Allen-Corner hypothesis).

III. It is due to direct stimulation of the endometrium by some substance liberated by the anterior hypophysis (a theory first advanced by Hartman, Firor, and Geiling[47]).

Before entering into a critical analysis of these three theories and citing other literature, we will emphasize that for the sake of precision the terms "menstrual function" and "menstrual flow" must be clearly differentiated.

As regards Theory I: Sturgis and Meigs[31] published most instructive microphotographs showing the changes in the endometrium from the proliferative phase, under estrin influence, into the "postovulatory, presecretory" (Hisaw) as soon as ovulation has occurred and corpus luteum effect begins. Knowledge of the fact that the endometrium, with formation of the corpus luteum, enters into the characteristic predecidual phase and with persistence of a corpus luteum of pregnancy develops into a true decidua, naturally led to the conclusion that involution of the corpus luteum of menstruation, that is, diminished supply of progestin, causes the disintegration of the predecidual mucosa and thus hemorrhage. This conception of the causation of the menstrual flow is well supported by certain experimental findings, of which more later on, and at least one common clinical observation, I think first reported by Halban many years ago. Removal of the ovary containing the last corpus luteum or deliberate excision of the corpus luteum incident to an abdominal operation almost invariably is followed by a menstruation-like flow within about forty-eight hours, independent of the time elapsed since the last menstrual bleeding.

Theory II applies chiefly to the anovulatory pseudomenstrual flows. From this viewpoint we can understand why Corner[10] does not ascribe to the corpus luteum any rôle in the actual causation of the flow, but finds its useful action limited to putting the uterus into a proper state for the implantation and nutrition of the fertilized ovum.

Kaufmann,[11, 12] Loeser,[14] Zondek,[5] Werner and Collier[48] among many others have convincingly shown that artificially two types of uterine hemorrhage can be produced, the one from an endometrium in the characteristic secretory phase, which always depends upon a definite dose of progestin (corpus luteum hormone), and the other from a merely hyperplastic endometrium when artificially supplied estrogen influence is more or less suddenly reduced or eliminated.

While there are at present no methods available of assaying the progestin contents of the circulating blood (Hartman), the opposite holds true for determining the estrogen levels, designed chiefly by Frank and his coworkers. They ascertained[49] that in the normal adult woman the estrogenic factor in the blood gradually increases to 25 M.U. per liter within one week of the anticipated flow and with its onset (within two to six hours) disappears from the blood. Considerable variations were observed by them in the amounts of estrogen eliminated in the urine with two periods of maximum excretion, the one in the middle of the interval (the theoretical time of follicle rupture) and the other in the week preceding the flow. The menstrual blood always contains large quantities of estrogenic substance. Fluhmann[23] made individual blood estrin curves for 12 normally menstruating girls. Out of 14 such

curves, 11 showed a peak between eight and eighteen days before onset of next flow. A second increase of estrin levels in the blood is seen in 5 of the curves within four days before or during the flow. In 2 instances occurred only one rise during the three days before flow, and in one case but traces of estrin or negative test were obtained throughout the whole cycle. Slight discrepancies in the findings of this series as compared with those of Frank and others, in the belief of Fluhmann, most probably are explained by a newer, more sensitive test used by him. Smith and Watkins[50] studied in two normally menstruating women the urinary output of estrogenic and gonadotropic hormones during two and four normal menstrual cycles, respectively. They admit that there is at present no method available to determine exactly the amount of gonadotropic factors in the urine of nonpregnant women. The follicle-stimulating hormone was consistently demonstrable only immediately before the flow, but maximal excretion, regardless of the length of the cycle, in every instance occurred on the twelfth or thirteenth day before onset of flow, almost exactly coinciding with the peak of estrin (folliculin) elimination in the urine.

Allen and coworkers[51] analyzed the urine of five adult chimpanzees for estrogenic content during various stages of the menstrual cycle. They found highest values at the time of genital swelling, the lowest at the time of uterine flow.

A fall of the estrogenic blood level, as previously mentioned (Theory II), is assumed to account for the anovulatory menstruation-like flow. Thus the hypothesis was advanced that also for the true menstrual hemorrhage the seemingly physiologic drop in estrogen and not the appearance of corpus luteum hormone represents the immediate cause for the endometrial bleeding. Strong evidence against any such assumption has been furnished by Kaufmann.[11, 12] He had previously shown that a typical secretory endometrium can be artificially produced only when the administration of a certain amount of folliculin is followed by a sufficient amount of progestin. He repeated this experiment on a castrated woman but continued with the introduction of large doses of follicular hormone also while giving the corpus luteum hormone. Nevertheless, there occurred one hemorrhage, the removed endometrium exhibiting the characteristic secretory phase. Thus he contradicted Clauberg's argument, that a flow from an artificially stimulated endometrium, in the experiments of Kaufmann and others, might have been due solely to the cessation of administration of the follicular hormone. In another patient Kaufmann injected large amounts of folliculin for several days before and also after removal, during operation, of a corpus luteum. Nevertheless, she began to bleed within two days after operation. In his belief these two experiments strongly support the idea that the true menstrual flow depends upon cessation of corpus luteum influence.

Theory III mentioned by Engle refers to the existence of a specific bleeding factor.

The bleeding, writes Hartman,[8] occurs "upon the withdrawal of estrin and corpus luteum hormones, when some yet unknown outside factor, probably pituitrin, brings about constriction of the blood vessels and necrosis of endometrial tissue, which is followed by sloughing of

the surface layer.'' He particularly emphasizes that it has been shown that the hypophysis probably is necessary for theelin action in relation to bleeding.[52]

Fluhmann[53] is willing to acknowledge that Allen's ''estrin deprivation theory'' offers an acceptable explanation of the bleeding in an anovulatory cycle, but he considers this theory inapplicable to the true menstrual flow, because, in his own studies, he found that it may occur also at a time when the amount of estrogenic substances in the blood is high, and that considerable rise and fall of these substances in the blood is found associated with amenorrhea. These facts induced him to believe that some other factors must also play a part in the origin of the true menstrual flow.

Analyzing ''endometrial findings in menstrual disorders,'' Anspach and Hoffman[54] met with several confusing facts in regard to the question of a ''bleeding factor.'' There is first the now well-known possibility of a normal menstrual flow coincident with regression of a corpus luteum but also of menstruation-like flow in the absence of a corpus luteum. Second, a corpus luteum may be formed and persist, resulting in an amenorrhea. Third, administration of hormonal products, so far available on the market, has a doubtful influence on the menstrual function of the adult woman. ''Thus the conclusion can be scarcely avoided, that there is some factor yet to be found to explain the uterine bleeding. Experiments apparently indicate that anterior pituitary hormones, as well as estrin and progestin, play a part in the bleeding mechanism, but just how, we do not know. It may be due to some positive mechanism thus far unexplained.''

Among several other articles dealing with this mooted question, we shall quote but the one recently published by Wilson and Kurzrok.[55] They agree with the conclusions of Hartman and coworkers that the bleeding per se is due to a special nongonadotropic hormone from the anterior pituitary, and offer the following hypothesis of a bleeding mechanism applicable to all functional or hormonal forms of uterine bleeding, normal and abnormal: There is an anterior pituitary hormone separate and distinct from the follicle-stimulating and luteinizing hormones. It is not gonadotropic but works directly on the endometrium. Its production is stimulated by the follicular hormone. Its activity is inhibited, but not destroyed, by progestin. When a certain concentration of this ''bleeding hormone'' has been reached, the actual onset of bleeding occurs, providing its action is not fully inhibited by corpus luteum hormones. The bleeding stops with the exhaustion of this hormone. To this hypothesis of Wilson and Kurzrok we must add that Witherspoon and Collins[56] even speak of the still unknown hormonal factor which controls cessation of the normal menstrual flow.

V. PERIODICITY OF MENSTRUAL FLOW

Extensive statistical investigations in regard to certain aspects of the ''safe period'' incidentally revealed the noteworthy fact that normal menstrual function is periodic but hardly ever regular. It would be impossible and useless to quote here all the data that have been published in the last few years, and it will be sufficient to show the striking agreement in information supplied from all parts of the world. Edward Allen[57] gives exact date records furnished by 110 pupil nurses of a training school, covering 1414 menstrual periods. The most noteworthy

fact revealed is the marked irregularity, even among 87 nurses who at the beginning of the study felt certain that they were "absolutely regular." As a matter of fact not one of this group menstruated regularly at a twenty-eight-day interval. Scipiades[58] used as his material 55 female students of both the philosophic and medical departments of a German university. He can only confirm the findings of others that absolute regular return of the flow is extremely rare. To identical conclusions comes King[59] analyzing 354 menstrual flows in 37 normal industrial and college women. Fluhmann[60] reports on a statistical study covering 747 cycles in 76 healthy California girls. He states: It was impossible to find any instance where numerous consecutive cycles were of the same length. It was impossible to group the subjects into twenty-eight, thirty, or twenty-one-day types. No basis was found for the conception that the cycle generally represents a multiple of seven days. Menstrual flows occur at all phases of the moon. A number of current ideas concerning regularity of the menstrual function, he concludes, will have to be reconsidered.

Ogino's graphed data show that only 0.7 per cent of his cases (Japanese women) were absolutely regular, 10 per cent varying from one to three days, 44 per cent up to ten days, while in 56 per cent the variations amounted to eleven days and more (quoted by Fluhmann).

Holt[61] limited his observations to women who asserted that their flows were "as regular as a clock," or "always on the same day of each month." Even with allowance of three days for variations in intervals, the "regular" ones did not approach anywhere the 90 per cent claimed by Knaus. Hardly one could be found to comply with Ogino's demand for 12 consecutive flows in identical intervals. Though not concerned here with the problem of the "safe period," we must refer to a paper by Latz.[62] In his series he found in 90 per cent variations from two to eight days, but since this method in his opinion is safely applicable as long as the variations between longer and shorter intervals do not exceed ten days, he considers 80 per cent of all women as regularly menstruating.

Richards[63] emphasizes that particularly valuable information can be gained by continued and uninterrupted recording of periods of the same woman extending over several years. In this manner can be revealed systematic variations in intervals according to seasons or subsequent to intervening pregnancies. In one of his patients who kept a menstruation calendar, the flows were less frequent in summer and more frequent in late fall. In another instance, flows came in shorter intervals in late spring and in longer intervals in late fall. Mueller[64] philosophically discusses the evident rhythmicity in various vital processes and the regular variations in the vegetative nervous system. Such variations beyond doubt are caused by seasonal changes and by the twenty-four-hour cycle of the full rotation of the earth around its axis with the alternation of day and night, but also are influenced by the revolving of the moon around the earth in a twenty-eight-day cycle, as is noticeable particularly in animal life.

In the opinion of Guthmann and Oswald[65] no doubt any longer can be felt concerning a time coordination of rhythmic variations of atmospheric and other extraterrestrial (cosmic) conditions to some of the various biologic processes which are rhythmic. However, it remains difficult to discover the more direct causal connections in regard to the rôle played, e.g., by the sun or possibly by the moon. In popular

opinion, varied and prompt effects of the lunar phases are often taken for granted, and scientific proof for such an effect in some respects is not entirely wanting. Thus one can easily understand the widespread belief in an intimate relation of the twenty-eight-day moon cycles to the menstrual cycles. Guthmann and Oswald carefully review the extensive literature which gradually has accumulated since Svante Arrhenius first endeavored to establish causal relations between lunar phases and pathologic phenomena in man (a question widely discussed again within the last few years). Studying the histories of 10,393 patients of the Gynecologic Service of the Frankfurt University Clinic, they ascertained that with marked frequency normal or unexpected onset of a menstrual flow occurs either at the time of a full or a new moon. "From a biologic viewpoint such an influence (of the moon) on the menstrual flow is entirely creditable. We know that, in spite of its dependence on spontaneous cyclic variations of endocrine activities, the menstrual cycle also is retarded or accelerated by many external factors and influences, among which we shall have to include a cosmic influence."

In conclusion, we shall mention a hypothesis recently propounded by Theobald.[66] "There is no rhythmical function of the body, apart from menstruation, which is not accepted as being controlled by a center in the brain." The regularity of the menses is a phenomenon that suggests a central rather than a haphazard hormonal control. On the basis of some clinical observations (that amenorrhea can be caused by mental strain, that the menstrual cycle can be changed by hypnosis or can be stopped by morphine, etc.), he evolves the theory that afferent stimuli to a menstruation center in the hypothalamus are provided by the ovarian hormones and by nervous stimuli from the generative organs and the cerebral cortex, while the efferent stimuli from the center operate through the anterior pituitary gland.

If this hypothesis is correct, he concludes, the correct method of treating menstrual disorders, provided ovaries and anterior pituitary are functioning normally, for the majority of cases is to treat the center directly by suggestion or indirectly by promoting the general well being by dietetic and hygienic measure.

VI. MENSTRUAL BLOOD LOSS

Normal menstrual blood does not coagulate. Most carefully planned studies of Dogliotti[67] furnish proof that this lack of coagulability is not due to the admixture of follicular or corpus luteum hormones but solely to the absence of both fibrinogen and thrombogen. Also Daniel and Florian[68] emphasize the difference between normal circulating and menstrual blood, and ascribe lack of coagulability of the latter to deficiency in fibrogen and richness in tryptic ferments. These writers claim to be the first to ascertain that just before and during the menstrual flow also the circulating blood temporarily becomes less coagulable. (We are not aware of any study in regard to possible differences in this respect between ovulatory and anovulatory uterine hemorrhages, though this point might prove of scientific and practical importance.)

Increased loss of blood is due either to a more profuse flow or its undue prolongation. In the opinion of Hirsch-Hoffmann[69] the latter condition is caused by unusually slow elimination of the menstrual endometrium, which then shows striking variations from the characteristic histologic picture. He ascribes prolonged menstrual flow to some deficiency in the involution of the corpus luteum.

Barer and Fowler[70] stress the striking discrepancy among writers in regard to the amount of actual blood loss, which is variously given as from 1 to 20 ounces, or between 20 and 500 gm. Most commonly Hoppe-Seyler's figure of an average of 37 c.c. is accepted. They used, on 100 normally menstruating women, an entirely new method. All blood was carefully collected on cellulocotton pads, and the material analyzed for iron. From the recovered amount of iron was figured the amount of hemoglobin, and from this the blood loss was calculated. Thus they arrived at the following conclusions: The blood loss varies between approximately 6.5 and 178.5 c.c., averaging 50.0 c.c., about one-half of the women losing approximately 23 c.c., and other half 68 c.c. The duration of the flow and the number of pads used convey only a very vague idea of the actual blood loss.

VII. PARTICIPATION OF VAGINA, CERVIX, AND TUBES IN MENSTRUAL CYCLE

A. *Vagina.*—The follicular hormone is primarily a growth hormone, which affects chiefly the female genital tract and the mammary glands. The wall of the vagina of rodents is the best indicator of such experimentally induced growth (Allen[7]) and on this fact is based the Allen-Doisy biologic test for estrogenic substances. Furthermore, the typical involutionary changes in the vagina during menopause as a result of cessation of normal ovarian activity are well known. In view of such evident relationship between vaginal mucosa and ovarian function, it seemed fully justified to assume that this mucosa in some form would participate in the cyclic changes of ovarian activity in the human female. Most writers give credit to Dierks[71] as having first, in 1927, established periodic vaginal epithelial changes incident to the menstrual cycle. He removed pieces of vaginal mucosa from about 30 women, and relating their histologic structures to the respective dates of last menstrual flow, he determined that the vaginal mucosa passes through a sequence of histologic alterations within each cycle.

It seems interesting to follow chronologically the variations of views expressed by successive investigators. Adler,[72] the coworker of Hitschmann, in 1928, fully confirmed the findings of Dierks and described the changes as follows: In the first half of the intermenstruum the vaginal epithelium proliferates, the flattened cells increase and cornify. In the premenstrual period a clearly differentiated layer forms in the most superficial part of the cornified zone, which disappears after the flow and is formed anew in the interval. This "functional layer" is particularly marked during pregnancy and is absent during amenorrheic periods of prepuberty, climacterium, puerperium, and lactation.

In 1929, Walter[73] states that definite cyclic changes occur in the vagina of the mouse but not in the human vagina. He agrees that the upper horny layer is cast off but denies that this takes place in any periodic manner. He emphasizes that different portions of the vaginal wall at the same time will show very dissimilar pictures in regard to this layer. He argues that the vaginal lining is not a true mucosa but epidermis, and as such shows in the usual manner casting off of the top horny layer with regeneration from the basal layer.

In the belief of Geist,[74] in 1930, the vaginal mucosa undergoes cyclic changes probably dependent on the ovarian hormone. At the present time, he states, it is difficult definitely to accord each picture its proper place in the cycle. "Naturally certain variations in ovarian and en-

dometrial cycles with some overlapping and with individual differences suggest that in some patients also in the vagina the same variable condition prevails."

Stieve[75] feels unable to accept Dierks' theory, because he not only found different pictures in the vaginal mucosa corresponding to the same phase of the menstrual cycle but was able to ascertain that similar structural changes occur also in the epithelial layers of the oral cavity and esophagus, both in men and women.

In 1933, Papanicolaou[76] definitely determined that the vaginal secretions of the human female change typically in the various phases of the menstrual cycle as he had previously established for certain animals. Rhythmic changes, coordinated with ovarian activity and ovulation, in the vaginal epithelium of a large group of monkeys were described in 1935 by Davis and Hartman.[77]

"Are There Cyclic Changes in the Human Vaginal Mucosa?" is the title of a recent (1936) contribution by Zondek and Friedmann.[78] Emphatically they answer this question in the negative. There are changes, often found to a varying degree in the same vagina, but they are not cyclic. In some cases of primary amenorrhea, histologic pictures are seen identical with those in women with normal ovarian function. Administration of estrogenic hormones, in the absence of normal ovarian activity, does not change the histologic structure of the vaginal mucosa (however, appearance of cornified squamous cells after administration of estrogenic substances to menopausal or castrated women has been recorded by Papanicolaou and Shorr.[79]) Zondek and Friedmann conclude with the apparently valid argument that recorded differences in the biologic reaction of the vaginal mucosa to cyclic ovarian activity are easily explained by the fact that in different species the vagina itself is embryologically developed in different manners.

Incidentally, we will mention that Fagioli[80] failed to discover any noteworthy changes in the pH of vaginal secretions in the course of the menstrual cycle, but, of course, he could not make these tests during the flow.

B. *Cervix.*—Some time ago R. Schroeder and Nuerenberger found that the mucosa of the uterine isthmus participates in the periodic changes of the endometrium, and this view is now rather generally held.

Emil Novak (in Curtis' *Obstetrics and Gynecology,* 1933, W. B. Saunders Co.) asserts that cyclic alterations have never been established for the mucosa of the cervical canal. Wollner[81] describes observations made on strips of cervical mucosa removed from time to time from the same women by means of a Hyams' electrode (cutting current of high frequency). He ascertained that, at least in some women, a definite histologic cycle exists.

As an expression of underlying structural changes has been accepted the observation of a definite thinning of the cervical mucus in the midinterval, usually interpreted as an additional factor favoring conception at this time. Séguy and Simmonet[82] used this phenomenon in an attempt to determine the time of ovulation. Assaying the estrogenic contents of the urine and inspecting during laparotomy the ovaries in about one-half of their cases, they were able to ascertain that the previously thick cervical mucus became thinner approximately coincident with the rupture of the mature follicle. Moench,[83] repeating Kurzrok's experiments in regard to the penetration of spermatozoids into the cervical secretions, agrees that this ability seems to be dependent on the

viscosity of the discharge. He feels, however, that the solubility of the cervical mucus varies at different stages of the cycle solely as a result of varying amounts of added secretions from uterine body and tubes. These latter secretions certainly are influenced by follicular hormones, and thus one might have to admit that there actually exists a relation between consistency of the cervical mucus and ovarian activity. As a matter of fact, the rubbery cervical plug during pregnancy has been explained as due to the absence of the solvent action of the combined tubo-uterine secretions.

C. *Tubes.*—In a paper, published in 1928, Novak and Everett[84] presented a careful review of the entire literature dealing with cyclic changes in the tubal mucosa. On the basis of extensive studies, they themselves had made, they arrived at the conclusion that, while the tubal mucosa does not normally participate in the bleeding phenomenon of menstruation, its epithelium exhibits definite cyclic changes comparable with those of the endometrium.

However, it seems that in the absence of an endometrium, the tubal mucosa is likely to bleed vicariously. This can be noticed in instances in which after a vaginal hysterectomy, a part of the preserved tube had been caught in the vaginal scar. Strassmann[85] utilized this capability of the tubal mucosa to bleed under ovarian influence for the purpose of restoring a functionating menstrual channel. We shall have to say more of this operation in a later chapter.

In 1929, Tietze[86] described in detail cyclic changes observed in 44 tubes removed from regularly menstruating women. Particularly marked are the alterations in the ciliated cells, which show greatest development at the fourteenth and fifteenth days of the cycle, that is, at the time when the ovum is extruded from the ruptured follicle and has to be transported to the uterine cavity. More recently Jaegerroos,[87] polemizing against a contrary view of Westman, insists that his own investigations definitely establish in the human female the participation of the tubes in the cyclic menstrual changes.

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(To be continued.)

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants by the American Board of Obstetrics and Gynecology will be held in various cities in the United States and Canada on Saturday, November 6, 1937.

The next general examination for all candidates (Groups A and B) will be held in San Francisco, Cal., on June 13 and 14, 1938, immediately prior to the American Medical Association meeting.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for these examinations must be filed in the Secretary's office not later than sixty days prior to the scheduled dates of examination.

The Chicago Gynecological Society

At the 1937 Annual Meeting of the Chicago Gynecological Society the following officers were elected:

George de Tarnowsky, President
David A. Horner, President-Elect
Julius E. Lackner, Vice-President
George H. Gardner, Treasurer
Edward Allen, Secretary
R. A. Lifvendahl, Pathologist
R. M. Grier, Editor

All communications concerning the publication of our Transactions should be addressed to Edward Allen, 55 E. Washington Street, Chicago, Ill.

Central Association of Obstetricians and Gynecologists

The Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists will be held October 14 to 16 at the Hotel Adolphus in Dallas, Texas. The guest speaker will be Dr. C. MacFie Campbell, Professor of Psychiatry at the Harvard Medical School. Dr. Campbell will speak on "Personal and Environmental Factors in Obstetrical and Gynecological Practice." The profession is cordially invited.

For further information apply to the Secretary, Dr. Ralph A. Reis, 104 S. Michigan Ave., Chicago, Ill.

International Congress of Obstetrics and Gynecology

Amsterdam, Holland, May 4 to 8, 1938

Attention is again called to this prospective gathering which promises to be a success from the standpoint of attendance, the Directors having had favorable responses from many sources.

Her Majesty, the Queen of the Netherlands, has graciously agreed to assume the patronage of the Congress.

Three main subjects have been listed for discussion at the stated morning meetings, namely eclampsia, thrombosis and embolism, hormones. The following have been invited to conduct the discussions:

I. Eclampsia.	
Pathogenesis	Dr. E. Klaften, Vienna.
Treatment	Dr. H. Vignes, Paris, and Prof. B. Stroganoff, Leningrad.
Eclampsia From a Geographical Standpoint of View	Prof. K. DeSnoo, Utrecht, and Prof. R. Remmelts, Batavia.
II. Thrombosis and Embolism.	
Diagnosis and Symptomatology	Prof. E. Alfieri, Milano.
Etiology	Prof. D. Dougal, Manchester.
Prevention and Treatment	Prof. E. Wichmann, Helsinki.
III. Hormones.	
Historical Review	Prof. G. Wagner and Prof. C. Kaufmann, Berlin.
Lectures on latest research	Dr. C. Hartman, Baltimore, and Prof. L. Brouha, Liége.

The afternoon meetings will be devoted to papers on a variety of subjects. Contributions to the program are still acceptable, subject to approval by the Directors.

Professor Dr. A. H. M. J. von Rooy, President
Dr. F. C. van Tongeren, Secretary
University Clinic for Obstetrics and Gynecology
Amsterdam, W., Holland.